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The American Heart Journal

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Original Communications

APNEA OR CONVULSIONS FOLLOWING STANDSTILL OF THE HEART*

CLINICAL AND EXPERIMENTAL OBSERVATIONS

P. FORMIJNE, M.D.
AMSTERDAM, HOLLAND

ONE of the most dramatic diseases known is the syndrome of Adams-Stokes caused by periodic standstill of the heart. The effect of sudden interruption of the supply of blood to all organs, more especially of that to the brain, is violent. About ten seconds after disappearance of the pulse, sudden loss of consciousness usually occurs, and later severe convulsions may appear. It may be assumed that convulsions are, under these circumstances due to anoxemia of the brain, for Kussmaul and Tanner showed in 1853 that convulsions, similar in nature to these, may be readily produced by clamping off its four main arteries. The sensitivity of the respiratory center to anoxemia is now well known and cessation of function of this center *during* long attacks of Adams-Stokes syndrome may not only be expected to occur theoretically but can sometimes actually be observed.

The present study is concerned with physiological disturbances, cerebral in origin, which occur not *during* the attack of cardiac standstill but almost immediately *after*. These cerebral symptoms consist of (a) cessation of respiration (period of apnea) and (b) convulsions. Doubtless similar phenomena have been observed by many authors, but they have been universally described as Cheyne-Stokes breathing. Most authors believe that Adams-Stokes attacks give rise to Cheyne-Stokes breathing through anoxemia of the brain. The most accurate account of this sort of apnea has been given by Griffith.[4] He describes a case in which the period of apnea had a constant and peculiar relationship to the period of standstill of the heart. It did not begin until after the

*A preliminary report of this subject was read in the Deutschen Gesellschaft für Kreislaufforschung, 8. Tagung. 1935.

From the Medical Service of the University of Amsterdam, Director, Professor Dr. I. Snapper.

period of asystole had passed off; there was occasionally even an interval of a few seconds between the end of asystole and the beginning of apnea. They never coincided in time. In other attacks, clonic muscular spasms of moderate violence came on a few seconds after return of the pulse. Similar phenomena have been described by Averbuck,[1] Dlugacz,[2] Grassberger,[3] and others.

Wenckebach and Winterberg[5] described a somewhat different sort of case in which a period of apnea *preceded* the period of asystole. They assumed therefore that apnea was the cause of asystole. They were able to show after Cheyne-Stokes breathing had almost disappeared that a voluntary pause of breathing induced a period of asystole, just as the spontaneous periods of apnea had done earlier in the illness. They explained the phenomenon by assuming that the action of anoxemia upon the automatic ventricular center leads to inhibition. A case similar to theirs in some respects will be described later in this article (Case 3). Since the descriptions of the attacks of asystole with apnea and convulsions and the theories as to their relationship did not seem satisfactory to us, we deemed it advisable to study the phenomena more carefully in an attempt to explain them on the basis of well-known and established physiological facts.

Views of the physiology of respiration, and of the relation between respiration and circulation have become clearer in the past few years. It has been shown that pulmonary ventilation is mainly regulated by the carbon dioxide content of the arterial blood. Increase in concentration of carbon dioxide in the blood results in increase in acidity to which the respiratory center responds by increasing the ventilation. In this way more carbon dioxide is given off through the lungs, and the normal arterial content of carbon dioxide and normal acidity of the arterial blood is reestablished. Conversely, decrease in the content of carbon dioxide in the arterial blood results in a shift in its reaction toward the alkaline side, decrease or even cessation of ventilation, retention of carbon dioxide and again reestablishment of the normal level of acidity of the blood. The respiratory center is, because of this mechanism, one of the most important factors in maintaining constant the degree of acidity of arterial blood. Heymans has found that chemical and physical stimulation of the carotid sinus may in addition have a profound influence upon the respiratory center.

A constant concentration of carbon dioxide in the arterial blood can be assured only by very accurate reciprocal adjustment between respiration and circulation. Disturbances of the carbon dioxide level in arterial blood are mainly due to three factors; changes in rate of (1) ventilation, (2) circulation, and (3) production of carbon dioxide. Either hyperventilation or decrease in volume of circulation alone, without change in the other two factors, will be followed by a lowering

of arterial carbon dioxide, and consequently a decrease in ventilation. It becomes clear then how a period of complete cessation of the circulation affects profoundly chemical equilibrium. A study of the nature of the disturbance seems to have been neglected by physiological and clinical investigators—at least I have not been able to find a single paper on this subject in the literature. My interest in the problem was aroused by clinical observation of five patients with complete heart block and attacks of Adams-Stokes disease. These observations suggested that disturbances of respiration or convulsions following temporary arrest of the circulation are due to the sudden arrival at the periphery of hyperventilated blood from the lungs ejected by the first few cardiac contractions following a period of asystole.

CLINICAL OBSERVATIONS

CASE 1.—A man eighty-three years of age was suffering from complete heart-block and frequent attacks of cardiac asystole. The sequence of events observed was as follows: First the pulse disappeared; some seconds later the patient said that an attack was coming on. Shortly afterward he became suddenly unconscious and

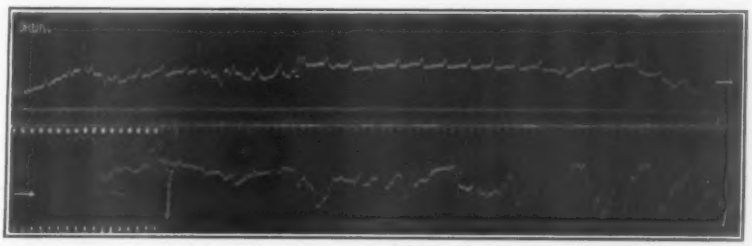

Fig. 1.—Case 1. Attack of standstill of the heart. The lower record is continuous with the upper. In the beginning total A-V dissociation is seen. After two contractions the ventricles cease beating, while the auricles continue. At the end of the upper record the string moves out of the field because of movement on the part of the patient (not a convulsion). The string reappears in the lower record, and shortly afterwards ventricular contractions start again. After the third, severe tonic and clonic convulsions cause continuous movement of the string.

turned very pale; respiration continued, and became deep and frequent. During the attack there were some movements, but no convulsions. Return of the pulse signalized the end of the attack. Some seconds later his face became very red. At the same time severe clonic contractions began, and lasted for about ten seconds (Fig. 1). This peculiar sequence of events was present in every attack that was observed.

CASE 2.—A man fifty-eight years of age with frequent attacks of Adams-Stokes syndrome was under observation during the four days preceding his death. At first, the same phenomena as in Case 1 were observed. After each attack of asystole, convulsions together with an intense flush of his face appeared after an interval of exactly six seconds. The fourth day, after an attack of cardiac standstill of unusually long duration (several minutes) a remarkable change was seen. Unconsciousness, not convulsions, followed the attack and persisted until death. In this state many shorter periods of asystole occured which, instead of being followed by convulsions, were followed at exactly the same interval (six seconds after cessation) by the period of apnea beginning simultaneously with flushing of the face, and lasting ten seconds.

CASE 3.—A woman seventy-six years of age with complete heart-block and occasional Adams-Stokes attacks was given barium chloride. During the use of this

medication many severe attacks occurred. When administration of the drug was stopped, the frequency of the attacks fell off to the former rate. After each attack a period of apnea was observed to occur coincident with flushing of the face. In this patient we were able to study the phenomenon by simultaneous records of respiration and of the electrocardiogram (Fig. 2).

CASE 4.—A man thirty-seven years of age in good health, except for painful mastitis, developed during examination sudden syncope with loss of consciousness,

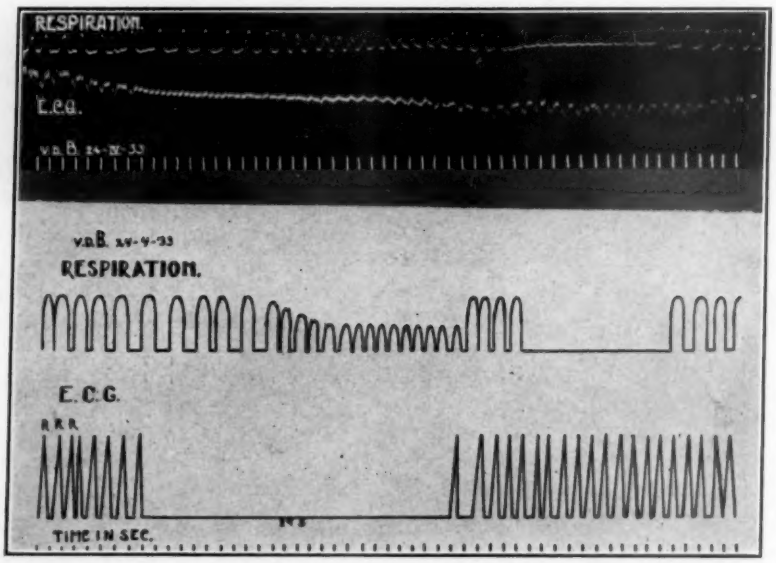

Fig. 2.—Case 3. An attack of standstill of the heart lasting twenty-four seconds is represented. Above, the original simultaneous record of respiration and electrocardiogram in a slow-moving film is shown. Below, the record is schematically drawn (auricular contractions are omitted). Note continuation of fast, shallow respiration during standstill of the heart. After return of ventricular contractions an immediate change of type of respiration (slower and deeper) occurs, probably reflex in origin. Some seconds later a period of apnea begins.

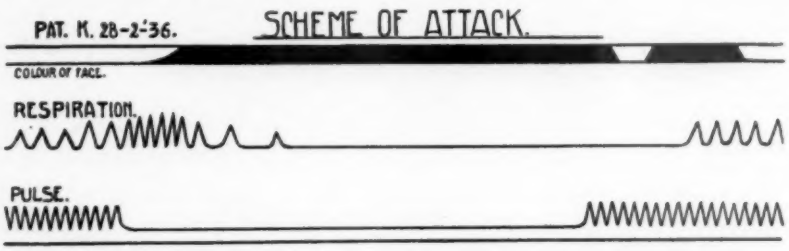

Fig. 3.—Case 5. Reconstruction of the sequence of events during and after an attack of Adams-Stokes syndrome, on the basis of observation. In the scheme for the color of the face, black indicates cyanosis, white the normal red color.

waxen pallor of the face, and disappearance of the radial pulse. After a short time there was a sudden flush of the face, and at the same time some symmetrical clonic contractions of the arms. The phenomena were identical with those observed in the first patient (Case 1). The reaction was somewhat less violent. Since this time, similar observations have been repeatedly made by different colleagues in instances of syncope following venepuncture.

CASE 5.—A woman forty years of age entered the neurological clinic because of frequent attacks of unconsciousness associated with convulsions. During the preceding six years these had been considered to be true epilepsy. Clinical observation showed that this diagnosis was not the proper one and that the attacks were due to Adams-Stokes attacks. By courtesy of Professor Brouwer and Dr. Drooglever Fortuyn I had the opportunity of observing an attack. It began with some acceleration of respiration, and disappearance of the radial pulse. Respiration continued for some time, then became slow, shallow, and stopped altogether. At this point both circulation and respiration had ceased. The face became gradually very cyanotic. Artificial respiration by compression of the thorax was tried without success. Then suddenly the radial pulse reappeared but apnea continued. A few seconds later there was a sudden red flush of the face followed rapidly by a return of marked cyanosis. Finally, respiration began and gradually the normal color of the face returned (Fig.

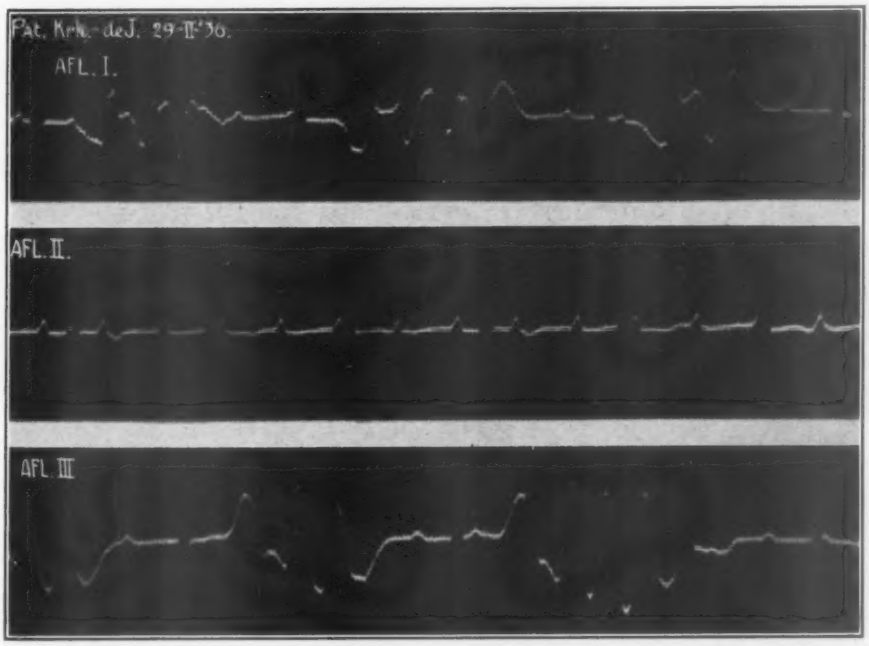

Fig. 4.—Case 5. Electrocardiogram made on Feb. 29, 1936. Total A-V dissociation. Series of ventricular premature beats.

3). An interpretation of this series of events is as follows: First, cessation of circulation with increased ventilation led to hyperventilation of the blood. Second, circulation and respiration both ceased. The hyperventilated blood stayed in the lungs without marked change. There was only a small gain in carbon dioxide and loss in oxygen from the metabolism of lung tissue. Third, reestablishment of circulation occurred with consequent transportation of the hyperventilated blood from the lungs throughout the body as indicated by the transient flush of the face. The respiratory center could not react as it had not yet recovered from prolonged anoxemia. Fourth, the hyperventilated blood from the lungs was followed by blood from the tissues laden with carbon dioxide and poor in oxygen; the latter passed the lungs unchanged as respiration was still absent. Fifth, recovery of respiration was stimulated by circulation of blood with increased content of carbon dioxide from the tissues. The patient was given ephetonine without effect and the next day was transferred to the medical service. An electrocardiogram (Fig. 4) was then obtained.

Complete heart-block was present and frequent ventricular premature beats occurred, sometimes in series of three or four. A tentative diagnosis of Adams-Stokes attacks due to ventricular fibrillation was made. It was confirmed later by a record obtained

Fig. 5.—Case 5. Attack of ventricular flutter lasting sixteen seconds. Immediately after the first isoelectric stretch (reestablishment of coordinated ventricular contractions) the occurrence of severe clonic convulsions is indicated by the violent movements of the string.

during an attack (second observed attack) accompanied by absence of the peripheral pulse (Fig. 5). The electrocardiogram showed a succession of very rapid electrical waves. It is doubtful whether these should be regarded as ventricular flutter or as fibrillation. The effect on the circulation was, as far as could be judged from clinical observation, the same as that of ventricular asystole. During the attack there was

continuation of respiration and absence of convulsions. Very soon after the end of the attack, marked in the electrocardiogram by the first isoelectric stretch, severe convulsions occurred.

That a period of apnea invariably followed an attack of cardiac standstill strongly suggested that the sequence was not fortuitous but the logical and necessary outcome of existing relations between circulation and respiration. During cardiac standstill the circulation must practically have ceased. The stagnant blood in the lungs was however continuously ventilated because respiration was uninterrupted. This blood therefore undoubtedly gained oxygen, probably to complete saturation, and lost large amounts of carbon dioxide. At the end of

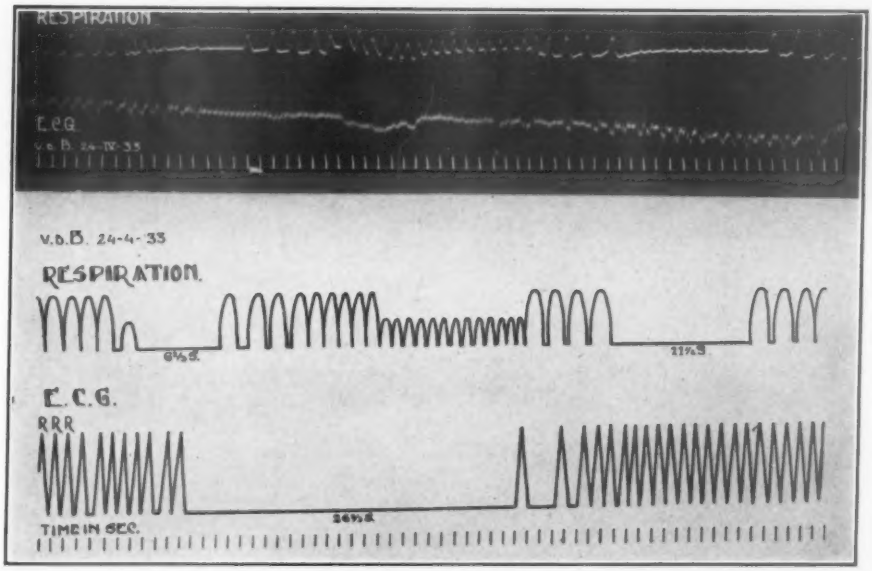

Fig. 6.—Case 3. An attack of standstill of the heart lasting twenty-six seconds is shown. It is preceded and followed by a period of apnea. Above, is the original record; below, a schematic drawing.

the period of cessation of circulation the lungs were apparently filled with intensely hyperventilated blood, rich in oxygen but very poor in carbon dioxide. The first few cardiac contractions would then suddenly distribute this blood throughout the body and what is more important, to the respiratory center as well. The reaction of the center would, of course, be to call forth a period of apnea until blood from the tissues, rich in carbon dioxide, arrived. We have seen that in the first patient, and also temporarily in the second, not apnea but convulsions were observed at this time. It seems probable that convulsions can also result from the reaction of the cerebrum to this abnormally hyperventilated blood.

The objection that the phenomena described were merely reactions of a disease or abnormal cerebrum may be raised. The first three

patients were obviously of advanced age and suffering, probably, from arteriosclerotic disease of the heart. Their brains may, therefore, not have been normal. This fact may be of some importance in Case 3, but it is plain that at least convulsions and flushing of the face, the two most frequently associated phenomena, may be seen in quite normal, perhaps only vasolabile, individuals (Case 4).

In addition to a period of apnea following each attack of asystole, one was inconstantly observed in Case 3 preceding the period of cardiac standstill (Fig. 6). It is evident that the same explanation will not suit both situations.

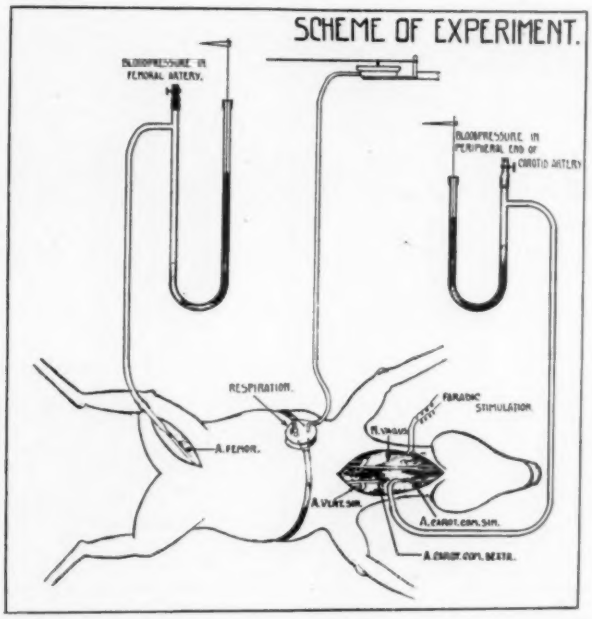

Fig. 7.—A rough sketch is shown of the arrangement of the manometers, the respiratory recorder, and stimulator for the experiments upon dogs and cats.

Another fact seems clear. The occurrence of convulsions or apnea and flushing of the face after cessation of the circulation is obviously not dependent on the cause of the cessation since they follow both cardiac asystole and ventricular fibrillation or flutter. One other point deserves comment. In Case 5 convulsions occurred not after the first very long attack but after the second shorter one. A possible explanation is that in the first observed attack (Fig. 3) hyperventilation was followed by apnea while the circulation was nonexistent; during this time (cessation of both circulation and respiration) hyperventilated blood may have remained in the lungs long enough for the metabolic processes there to produce enough carbon dioxide and probably lactic acid partially to counteract, by diminishing the alkalinity of the blood, the effect of the preceding hyperventilation.

So far argument has been built exclusively upon clinical observation and deduction. More convincing evidence for the theory that the observed phenomena are due to sudden distribution of the hyperventilated stagnant blood in the lungs is difficult to obtain from the study of patients because individuals with this disorder are rare, and also

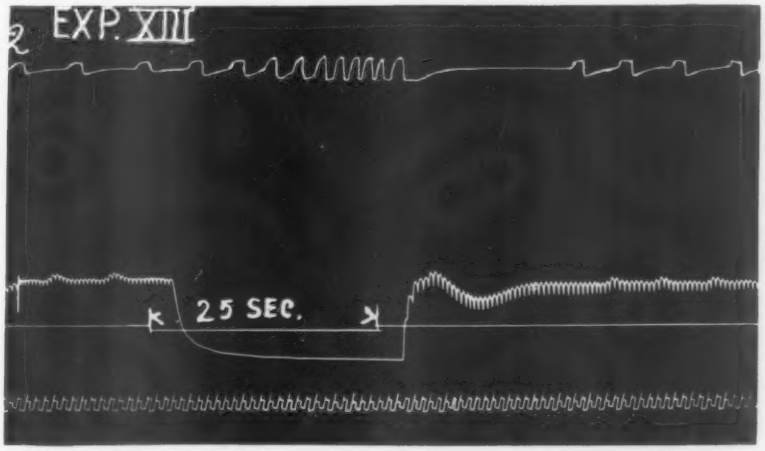

Fig. 8.—Experiment XIII. Dog in morphia-pernocton narcosis. Upper curve—respiration. Lower curve—tension in femoral artery. A record of standstill of the heart for twenty-five seconds is shown. After contractions of the heart return, a period of apnea occurs. In this figure and in Figs. 9-15, inclusive, cardiac standstill was induced by faradic stimulation of the peripheral end of the right vagus nerve.

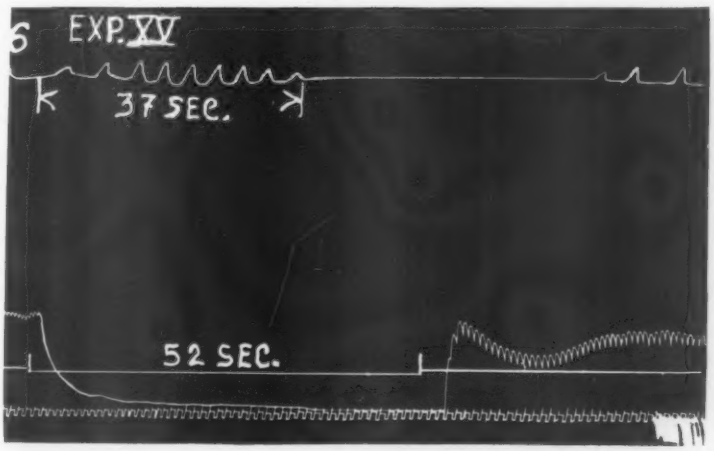

Fig. 9.—Experiment XV. Dog in morphia-pernocton narcosis. A record of standstill of the heart for fifty-two seconds is shown. Apnea begins during cardiac standstill.

because other mechanisms, for example, reflexes from the carotid sinus, may under these circumstances play a part. An attempt was therefore made to reproduce the phenomena in animals.

In dogs, temporary cardiac asystole can often be obtained after isolation and section of the right vagus nerve, through faradic stimulation

of the peripheral end (Fig. 7). Asystole of less than about ten or fifteen seconds' duration was not followed by disturbances of the respiration but when it lasted from fifteen to thirty-five seconds a well-marked period of apnea regularly followed it just as in Adams-Stokes attacks in patients (Fig. 8). When periods of asystole exceeded thirty-five to forty seconds, apnea started *during* them, and lasted some time after recovery of the circulation (Fig. 9). This type of apnea, namely, that which began *during* standstill of circulation, was

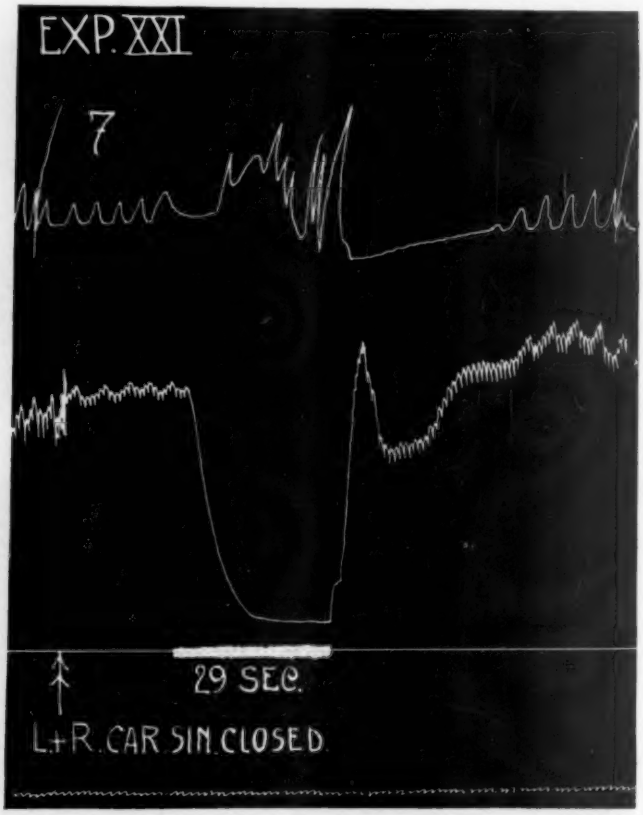

Fig. 10.—Experiment XXI. Dog in morphia-pernocton narcosis. Occlusion of all blood vessels leading to and from both carotid sinuses was completed at arrow. Standstill of the heart for twenty-nine seconds is still followed by a period of apnea.

attributed to prolonged anoxemia of the respiratory center. It was observed also on one occasion in a patient (Case 5). The apnea occurring after asystole of moderate duration (fifteen to thirty seconds) was subjected to further analysis.

Experiment I.* When both carotid sinuses were excluded from the circulation by clamping off all the branches to and from it, the period of apnea appeared in the same manner as before clamping (Fig. 10). This experiment was repeated in

*This numeration of experiments is made for convenience and does not correspond with the numbers of the actual experiments mentioned in the figures.

different dogs and seems to justify the conclusion that the period of apnea is not dependent upon carotid sinus reflexes.

Experiment II. When the carotid and vertebral arteries on both sides were isolated and clamped, almost no effect was observed on respiration in the narcotized animals. Life was possible for a very long time and Kussmaul-Tanner convulsions were not seen. The collateral circulation furnished apparently adequate nourishment for the brain so that loss of cerebral reflexes did not occur. Heymans has shown that some cerebral centers, including the respiratory center, can endure prolonged anoxemia and recover. A very small circulation can maintain the respiratory mechanism intact.

The effect of the collateral circulation on the maintenance of arterial pressure to the brain was measured by recording the pressure in the *peripheral* end of a carotid artery, before and after clamping the three other principal arteries leading to the

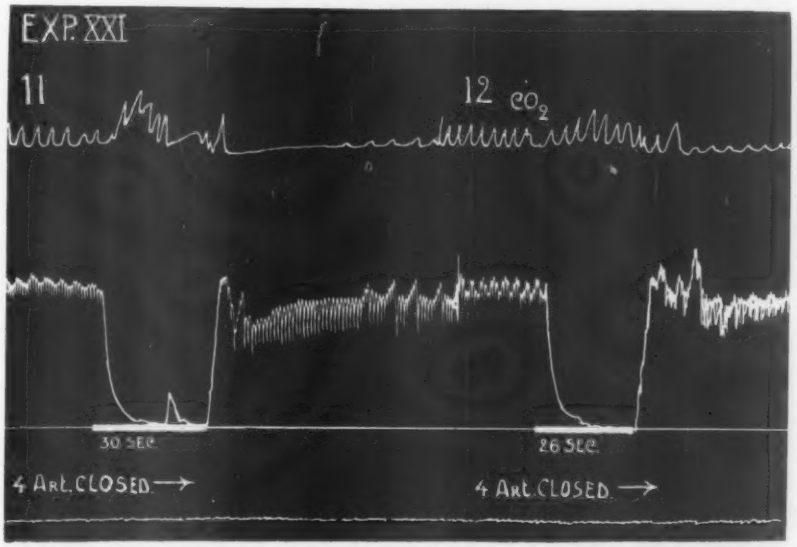

Fig. 11.—Experiment XXI. Dog in morphia-pernocton narcosis. Both carotid and vertebral arteries were clamped before the experiment. During inhalation of oxygen, asystole for thirty seconds (interrupted by one ventricular contraction) is followed by apnea (*11*). During inhalation of a mixture of oxygen and 5 per cent carbon dioxide asystole for 26 seconds is not followed by apnea (*12*).

brain. In dogs the pressure here is only about 20 mm. Hg before clamping the arteries and is extremely low afterwards. Now when cardiac contraction was inhibited by faradic stimulation while the four arteries to the brain were clamped, apnea still occurred after the period of standstill (Fig. 11). Apnea was therefore not the result of a sudden rise of blood pressure in the brain or in the carotid sinus since the rise was, in this experiment, insignificant.

Experiment III. The effect of inhalation of a mixture of 5 per cent carbon dioxide and oxygen on the appearance of apnea after vagal inhibition of the heart was studied, because this concentration of carbon dioxide prevents loss of the gas from the blood resting in the lungs. Its use regularly prevented the occurrence of apnea while inhalation of oxygen alone failed to do so (Figs. 11, 12, and 13).

Experiment IV. Direct proof of the passage of hyperventilated blood through the body was obtained by taking samples of blood from the carotid artery immediately after the period of asystole. The color of this blood was redder than

normal arterial blood; the carbon dioxide content was much decreased. For example hyperventilation was sufficient to reduce the carbon dioxide content of the arterial blood more than 4 volumes per cent (from 49.04, 49.09 to 44.88, 44.83 volumes per cent).

In a few experiments mild clonic contractions were observed during the period of apnea, analogous to the convulsions observed in patients with Adams-Stokes

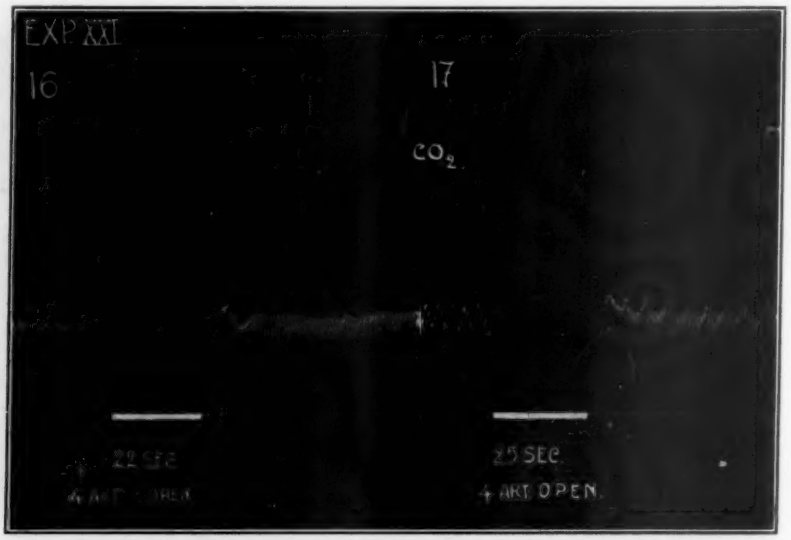

Fig. 12.—Experiment XXI. Dog in morphia-pernocton narcosis. All arteries to the brain are open. Inhalation of oxygen has no influence on the period of apnea (*16*) following cardiac standstill, while inhalation of mixture of oxygen and 5 per cent carbon dioxide makes it disappear (*17*).

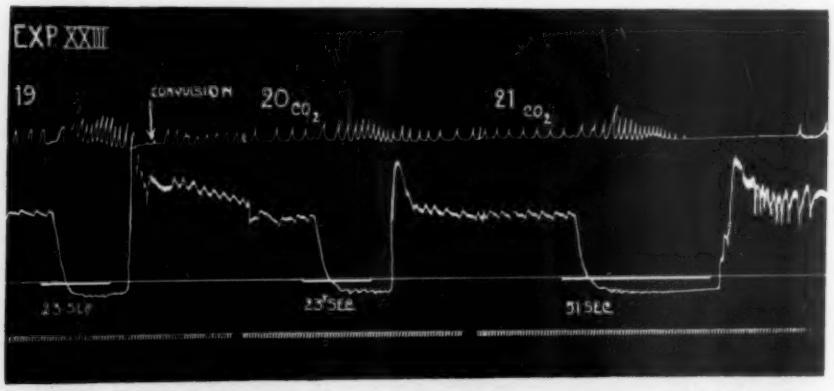

Fig. 13.—Experiment XXIII. Dog in morphia-pernocton narcosis. Asystole for twenty-three seconds during inhalation of oxygen was followed by apnea and mild clonic contractions (*19*), but asystole for the same period of time during inhalation of oxygen with 5 per cent carbon dioxide was followed neither by apnea nor clonic contractions (*20*). When asystole lasted for fifty-one seconds during inhalation of oxygen with 5 per cent carbon dioxide, apnea appeared before cardiac contraction commenced (*21*).

syndrome (Fig. 13). Experiment IV shows that during standstill of the heart hyperventilation and marked loss of carbon dioxide do occur in the blood which comes to rest in the lungs. Experiment III indicates that hyperventilation plays an important rôle in bringing about the period of apnea observed to occur after

recovery of the heart beat. It should be emphasized that the results were not uniform in Experiment III. In most instances, however, the periods of apnea failed to occur during inhalation of oxygen with 5 per cent carbon dioxide. Sometimes reflexes of the carotid sinus apparently played an additional rôle (Fig. 14). In the same experiment a short period of apnea still occurred after bilateral vagot-

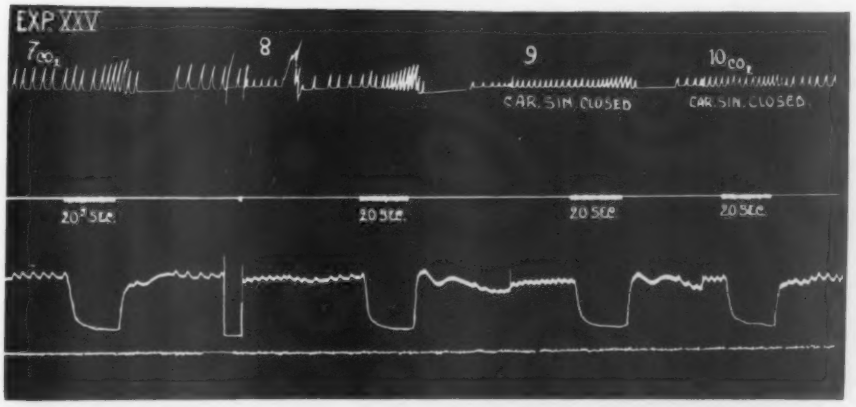

Fig. 14.—Experiment XXV. Dog in morphia-pernocton narcosis. In this experiment asystole during inhalation of oxygen and carbon dioxide, as well as during inhalation of oxygen was followed by apnea (*8*). After clamping all vessels to and from the carotid sinus, during inhalation of oxygen, asystole was still followed by apnea (*9*) but inhalation of oxygen and 5 per cent carbon dioxide prevented its appearance (*10*).

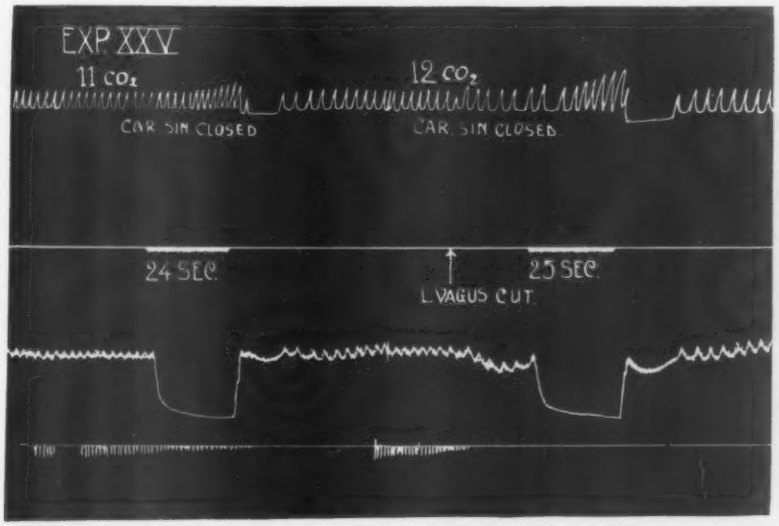

Fig. 15.—Experiment XXV. Continuation of Fig. 14. During occlusion of both carotid sinuses and inhalation of carbon dioxide, a longer period of asystole (twenty-four seconds) was again followed by a small period of apnea (*11*). Even when bilateral vagotomy was performed in combination with the above procedure, asystole (twenty-five seconds) was still followed by apnea (*12*).

omy, elimination of both carotid sinuses and inhalation of 5 per cent carbon dioxide mixture (Fig. 15). The reason for apnea was not clear in this instance.

Vagal stimulation for obtaining cardiac asystole had the obvious disadvantage that it did not resemble the cause of the Adams-Stokes attacks in man. It was possible too,

although very improbable, that vagal stimulation of the lungs influenced the phenomena studied. It seemed advisable, therefore, to bring about functional cardiac standstill in another way. Direct faradic stimulation of the heart initiates ventricular fibrillation which may recover spontaneously. The procedure is not useful in dogs, as spontaneous recovery is very rare. In cats, however, periods of ventricular fibrillation of the desired length can readily be induced by short periods of faradic stimulation (one to two seconds). The influence of vagal stimulation *during* cessation of the circulation is, in this way, eliminated.

Experiment V. It was found that ventricular fibrillation of moderate duration (twenty to thirty seconds) was followed regularly by a period of apnea, but when

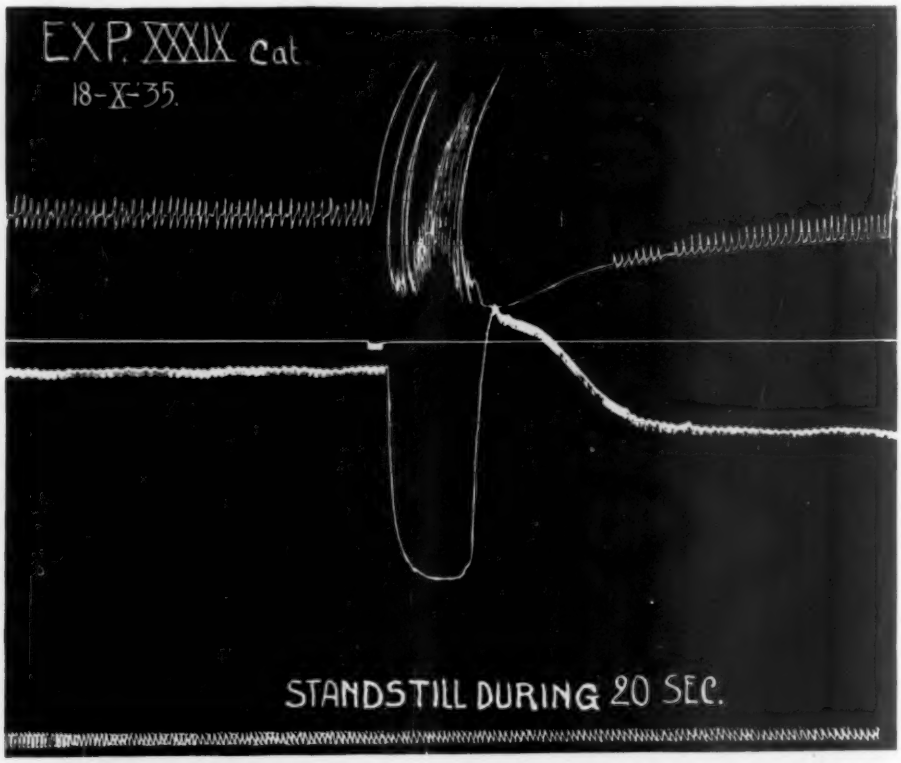

Fig. 16.—Experiment XXXIX. Cat in pernocton narcosis. Direct faradic stimulation of the heart for seventy-two seconds resulted in ventricular fibrillation (proved by electrocardiographic tracings in other experiments). After spontaneous recovery of coordinated ventricular contractions, apnea occurred.

it lasted longer (more than thirty-five to forty seconds) apnea began during the period of fibrillation just as in the experiments in dogs where asystole was produced by vagal stimulation.

Exact analysis of the period of apnea in cats presented greater difficulties than it did in dogs, for two reasons: (1) In each animal only a small number of experiments could be carried out, usually not more than three; (2) the duration of ventricular fibrillation could not be regulated. Spontaneous recovery had to be awaited. In some experiments inhalation of 5 per cent carbon dioxide mixture shortened the period of apnea, but did not make it disappear. A clear statement of its effect on apnea in this type of experiment cannot yet be made. Often slight

clonic cramps were observed during the period of apnea similar to those seen in dogs. Before passing on to the general discussion it appears desirable to point out that the mechanism responsible for cessation of the circulation, i.e., ventricular fibrillation, in these cats was similar to that observed in Case 5.

DISCUSSION

In summarizing the sequence of events which follow transient cessation of the circulation, it becomes plain that no matter what the method used to stop the circulation, either convulsions or apnea alone follow (Table I). In a few of the animal experiments apnea was combined with mild convulsions. The relation between these two different effects requires analysis.

TABLE I

CEREBRAL SYMPTOMS FOLLOWING TRANSIENT CESSATION OF THE CIRCULATION

	APNEA	CONVULSIONS
A. Adams-Stokes syndrome		
Patient 1	0	+
Patient 2—during consciousness	0	+
during coma	+	0
Patient 3	+	0
Patient 5—(ventricular fibrillation)	0	+
B. Syncope by fright or pain in healthy individuals		
Patient 4	0	+
C. Experimental standstill of the heart		
First by faradization of the vagus nerve in dogs	+	±
Second by direct faradic stimulation of the heart in cats (ventricular fibrillation)	+	±

1. As it has been shown that the occurrence of hyperventilated blood in the lungs leads necessarily to apnea after the attack, it may be assumed that apnea is also present during convulsions, but that it cannot be clearly observed because of the violent muscular movements.

2. The occurrence of convulsions when hyperventilated blood reaches the brain is, to a large extent, dependent upon the state of the brain and the degree of consciousness. This is demonstrated most clearly in Case 2: convulsions occur after the attacks during consciousness but are absent during coma. The occurrence of convulsions in "healthy" individuals after syncope, and their absence or mildness during narcosis in animals, is additional evidence that the state of consciousness is important. That mild convulsions occur occasionally during narcosis makes analysis difficult. Convulsions could probably be readily reproduced by vagal inhibition of the heart in non-narcotized animals but the experiment is scarcely justified.

It is certain that the convulsions begin at the precise moment that hyperventilated blood reaches the brain. The conclusion is therefore drawn that these convulsions are probably caused by the action of hyperventilated blood with its loss of carbon dioxide and the attendant

alkaline reaction on the brain. Some support of this view can be found in the increase of reflex irritability and the production of epileptic fits known to follow hyperventilation. Inhalation of the oxygen plus 5 per cent carbon dioxide gas mixture should in this case relieve the convulsions. The administration of this mixture during attacks to patients in whom convulsions ordinarily follow the attack will perhaps settle this point. The possibility that sudden excess of oxygen, reaching brain cells that have been anoxemic, is responsible for the convulsions, cannot be excluded.

The importance of local hyperventilation of the stagnant blood in the lungs in standstill of the heart has been demonstrated in the preceding observations and experiments. Now in sudden slowing of the circulation, hyperventilation of the blood must also occur if respiration does not diminish. This hyperventilated blood is transported to the respiratory center and if the level of carbon dioxide has been sufficiently reduced apnea will occur. Attacks of Adams-Stokes syndrome are often preceded by slowing of the rate. In the third patient the short periods of apnea which preceded attacks may conceivably be explained by slowing of the circulation. Proof for this tentative explanation cannot be offered.

It is unlikely that periodic breathing of the Cheyne-Stokes type can be explained by this mechanism. In simultaneous records of respiration and electrocardiogram slowing of the rate preceding the apneic phase was not observed. The gradual waxing and waning of respiration in Cheyne-Stokes breathing is, moreover, not seen in the periods of apnea caused by local hyperventilation, where there is an abrupt end and beginning of respiration. In chronic slowing of the circulation, hyperventilation in the lungs is counterbalanced by many factors; but it should be emphasized that slowing of the circulation through the lungs can of itself never lead to anoxemia of the arterial blood.

SUMMARY

1. In patients with complete heart-block and attacks of ventricular asystole, or with ventricular fibrillation, apnea or convulsions were observed to occur *after* the attack.

2. In healthy persons mild convulsions were observed to follow syncope due to emotion.

3. In narcotized animals in which cardiac standstill was induced by vagal inhibition, or ventricular fibrillation was caused by faradic stimulation of the heart, apnea was observed to occur *after* recovery of the heart.

4. Convulsions occurred only during consciousness. They were not observed in individuals in coma or in narcotized animals.

5. It was shown that during cardiac standstill continuance of respiration hyperventilates the blood in the lungs which is transported, on recovery of the heart, throughout the body and the respiratory center. It was furthermore demonstrated in animal experiments that this mechanism is mainly responsible for the period of apnea for, when oxygen and 5 per cent carbon dioxide were inhaled, apnea failed to occur. Carotid sinus reflexes and other mechanisms may, however, occasionally play an additional rôle.

6. Convulsions were therefore ascribed to the action of hyperventilated blood upon the brain. Further analysis was not possible.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING WITH ALTERATIONS OF POSTURE FROM RECUMBENT TO STANDING POSITIONS

LOUIS H. SIGLER, M.D.
BROOKLYN, N. Y.

IN 1935, Leimdörfer[1] observed changes in the T-wave, from positive to isoelectric and to negative coincident with alteration of posture from standing to recumbent. He attributed these electrocardiographic changes to latent and clinically undetectable cardiac disease.

I have found no other references in the literature to electrocardiographic observations on alteration of body posture from recumbent to standing, although many such studies in other postures have been recorded. I have therefore carried out such observations in a series of 100 consecutive cases that came to my office. Tracings were taken in the three standard leads with the patient in the dorsal recumbent posture. With the electrodes still connected, the patient was then made to stand up and the tracings were repeated several minutes after adjustment to change in posture. In some cases tracings were also taken with the patient in the sitting posture, supported by a back rest at an angle of about ninety degrees, and with the legs in a horizontal position. In most cases the fourth lead was also employed.

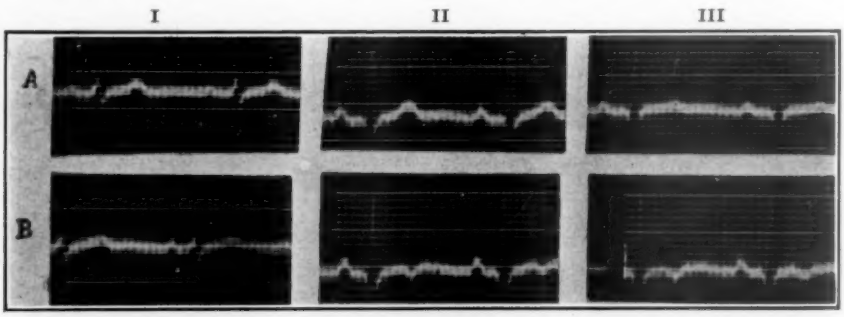

Fig. 1.—Changes in the T-wave in Leads II and III on change in posture. No appreciable changes in the QRS complexes. *A*, recumbent; *B*, standing. The electrocardiogram was obtained from a normal heart.

The cases were divided into Group 1, consisting of individuals with normal hearts, and Group 2, consisting of those showing gross cardiac disease. The electrocardiograms were analyzed by calculating the angles of the electrical axes of the QRS complexes and the T-waves, obtained in the various postures. From these, the directions and therefore any rotation of the electrical axes were ascertained. In cases where the

fourth lead was also employed, the differences in the voltage of the various components of the initial and terminal ventricular complexes were employed to gauge any changes that might occur.

RESULTS

The findings bring out very interesting facts which may prove to be of value in the interpretation of the electrocardiogram as an aid in

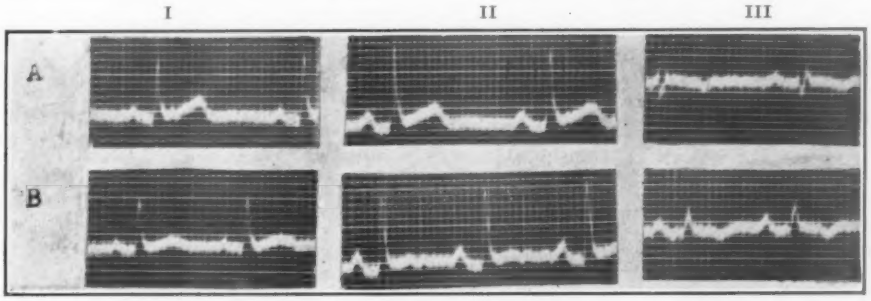

Fig. 2.—Change in T-wave in all leads and some shift in the axis of the QRS complex on alteration of posture. *A*, sitting; *B*, standing. Electrocardiogram obtained from a patient exhibiting the anginal syndrome in a mild degree.

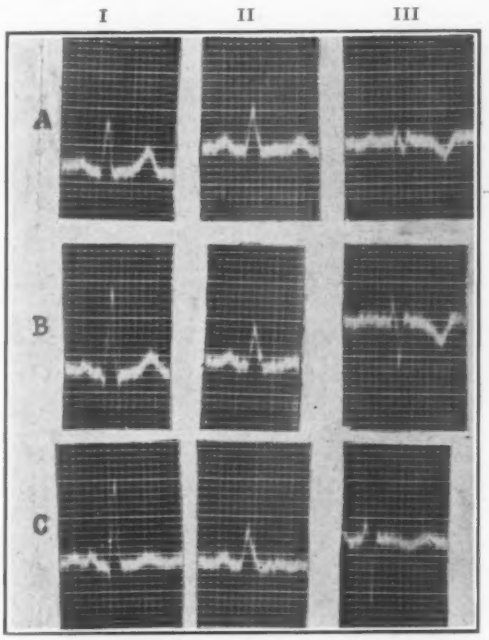

Fig. 3.—Progressive shift of the axis of the QRS complexes and changes in the T-waves on alteration of posture. *A*, recumbent; *B*, sitting; *C*, standing. Case of arteriosclerotic heart disease.

diagnosis. In many patients with perfectly normal hearts, there were definite and distinct changes noted, both in the QRS and in the T-waves, on alteration of posture from the recumbent to the standing, and even

on change from the recumbent to the sitting and sitting to standing position. The changes in some cases were so marked as to make the

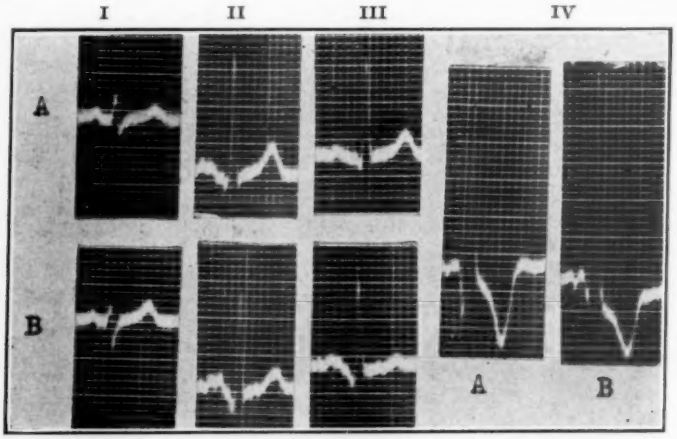

Fig. 4.—Rotation of the electrical axis of the QRS complex to the right and of the T-wave to the left and diminished voltage of the Q- and T-waves in Lead IV on alteration of posture. *A*, recumbent; *B*, standing. Case of mitral valvular disease, rheumatic.

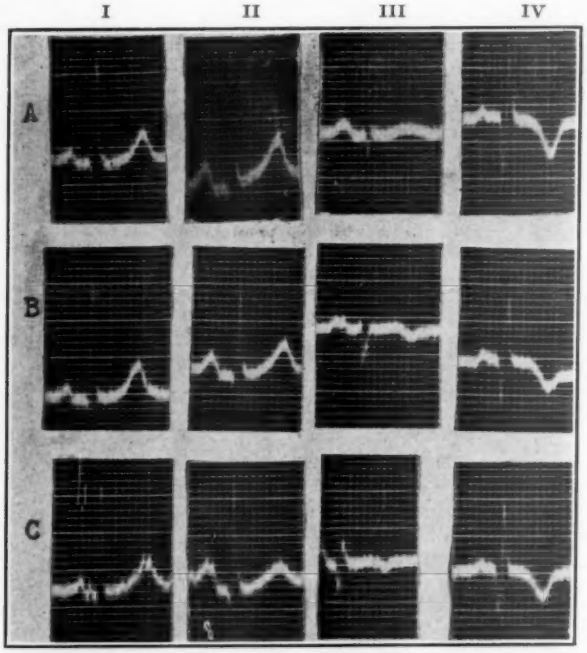

Fig. 5.—To-and-fro shifting of the electrical axis of the QRS complexes and the T-waves on alteration of posture. *A*, recumbent; *B*, sitting; *C*, standing. Case of thyrotoxic heart disease.

electrocardiogram appear abnormal and to lose its identity with those taken in the other postures in the same case. Individuals with abnormal hearts showed no greater changes than those with normal hearts.

In some cases changes occurred only in the T-wave, as shown in Fig. 1. The changes in these cases consisted of diminished voltage, flattening or actual conversion from a positive to a negative phase in one or more leads. This usually occurred in the third lead or in the third and second leads. In other cases there were concomitant changes in the QRS complexes with the T-wave changes, as shown in Fig. 2. Many showed shifting of the electrical axis of the QRS complex in various directions as well as changes in the T-waves producing alterations in their electrical axes, as shown in Figs. 3, 4, and 5. The axis shift of the initial and terminal ventricular complexes occurred either in the same direction or in opposite directions. If in the same direction, the amount of shift was not proportionate. If premature contractions were present, their voltage change was usually different than that of the normal complexes, as shown in Fig. 6.

A summary of the entire series of cases showing the changes of direction of the electrical axes among the normal and diseased hearts is given

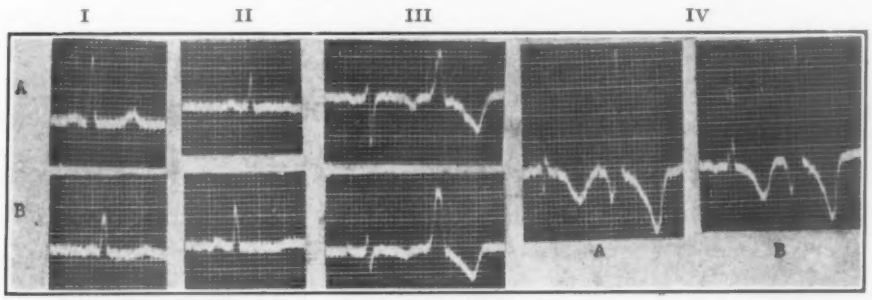

Fig. 6.—Diminished left axis shift of the QRS complex and change in voltage of T-wave with alteration of posture; also changed voltage of the ventricular premature contraction and the QRS complex in Lead IV. *A*, recumbent; *B*, standing. Case of hypertensive heart disease.

in Table I. It will be noted that a greater number of cases show shifting of the electrical axis of the QRS complex to the left in diseased hearts than in normal ones. The total number of cases showing any shifting, whether to the left or right, is the same in the normal as in the diseased hearts. Thus the differences in the behaviour of the normal group as compared with the diseased group is merely a difference in the direction of the shift. In the normal heart there is a greater tendency of the electrical axis to shift to the right while in the diseased heart the tendency is to the left. The T-wave, on the other hand, has a greater tendency to have its axis shift to the left in the normal and to the right in the diseased heart, on change from the recumbent to the standing posture. There is definitely a smaller number of cases showing a shift in the electrical axis of the T-wave than of the QRS complex with alteration of posture, in both normal and diseased hearts.

The degrees of the angles of the electrical axes in the three standard leads occurring with alteration of posture in the entire group of 100

TABLE I

ROTATION OF THE ELECTRICAL AXIS WITH CHANGE IN VARIOUS POSTURES

Number of cases showing changes in the direction of the electrical axes with different changes in posture. In the fourth column of each group is given the percentage of records showing changes of the electrical axis.

	RECUMBENT TO STANDING								RECUMBENT TO SITTING								SITTING TO STANDING							
	QRS				T				QRS				T				QRS				T			
	TO LEFT	TO RIGHT	NONE	PER CENT	TO LEFT	TO RIGHT	NONE	PER CENT	TO LEFT	TO RIGHT	NONE	PER CENT	TO LEFT	TO RIGHT	NONE	PER CENT	TO LEFT	TO RIGHT	NONE	PER CENT	TO LEFT	TO RIGHT	NONE	PER CENT
Normal hearts	7	14	10	67.7	9	1	21	32.2	2	3	4	55.5	3		6	33.3	2	5	4	63.6	2	2	7	36.3
Abnormal hearts	18	14	22	59.2	12	14	28	40.7	6		5	54.5	2	2	5	44.4	8	6	11	56.0	1		24	0.4

cases are recorded in Table II and Fig. 7. Case numbers 1 to 33 represent normal hearts, and 34 to 100, abnormal hearts. The fourth lead changes are also shown. It will be noted that the greatest changes in degree of the angles occur on alteration of posture from the recumbent to the standing. Alteration of posture from recumbent to sitting showed less change while that from sitting to standing, the least. The shift of the electrical axes of the T-waves was less marked than that of the QRS complexes.

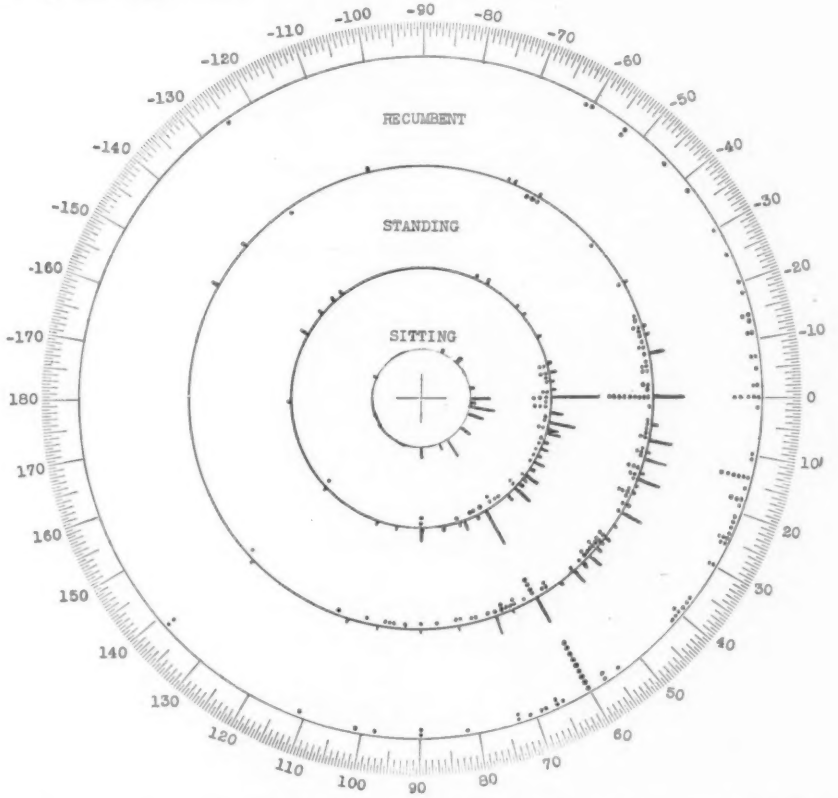

Fig. 7.—Graphic representation of the number of cases showing varying degrees of electrical axis deviation in the recumbent, standing, and sitting postures. Dotted lines represent axes of the QRS complexes, one dot per case. Solid lines represent axes of the T-waves, calibrated on a scale of 0.5 mm. per case.

DISCUSSION

It has been known for many years that changes occur in the electrocardiogram with alterations of posture from the dorsal recumbent to the left or right lateral recumbent and the sitting positions. Also displacement of the heart by pneumothorax, hydrothorax, massive adhesion, and other conditions are known to produce changes. Shifting of the electrical axis did not correspond in many cases with change in the anatomical axis of the heart occurring with alteration of the body posture. Thus, Meek and Wilson,[2] Nathanson,[3] Treiger and Lundy,[4]

TABLE II*

CASE NO.	DEGREE OF ANGLE OF ELECTRICAL AXIS (ANGLE ALPHA)						LEAD IV IN 0.1 MV.								
	QRS			T-WAVE			LYING			SITTING			STANDING		
	LYING	SITTING	STANDING	LYING	SITTING	STANDING	Q	R	T	Q	R	T	Q	R	T
1	60		68	49		60		10	-2					12	-3
2	40		40	44		44					No change				
3	73		73	0		- 2	5	10	-4				4	11	-3
4	13		76	60		39					No change				
5	66		60	16		16					No change				
6	54		49	46		46	5	8					1	10	
7	21		39	16		7		4	-6					5	-7
8	14		14	71		71					No change				
9	39	43	58	60	60	60		12			10			13	
10	71	66	66	60	60	60					No change				
11	57	57	57	60	60	60					No change				
12	57		66	60		60									
13	68	74	80	67	39	60									
14	82		94	71		41									
15	16	4	24	30	0	0	15	7		14	8		20	10	
16		0	0		- 7	- 7					No change				
17		4	8		41	41					No change				
18	41		41	49		49									
19	42		42	11		11	13	11	-11				12	12	-7
20	24		28	0		0		7	- 4					8	-3
21	26		26	0		0					No change				
22	60		41	49		11	8	7		6			7	6	
23	19		21	11		11	12	5					8	6	
24	14	14	-13	23	23	19					No change				
25	- 2		- 2	44		44	13	7					14	8	
26	38		39	16		16					No change				
27	-14	-14	-14	24	24	24	3			3			1		
28	14		18	43		36					No change				
29	25		20	0		0									
30	2	2	10	60	60	30		13	-7					15	-9
31	14		13	0		0	4						7		
32			25	44		44		19						24	
33	-25	-15	-16	44	14	35									

*Case numbers 1 to 33 represent normal hearts.
Case numbers 34 to 100 represent diseased hearts.

TABLE II—CONT'D

CASE NO.	DEGREE OF ANGLE OF ELECTRICAL AXIS (ANGLE ALPHA)						LEAD IV IN 0.1 MV.								
	QRS			T-WAVE			LYING			SITTING			STANDING		
	LYING	SITTING	STANDING	LYING	SITTING	STANDING	Q	R	T	Q	R	T	Q	R	T
34		57	69		60	60				No change					
35		43	43		0	0				No change					
36		- 9	- 9		-44	-44				No change					
37		67	67		44	44				No change					
38		54	44		90	90				No change					
39		- 8	-21		73	73	6-7	6					-9	4	
40	-20		-20	-11		16				No change					
41	0		- 7	60		90	13	19-21					10	21-22	
42	11		0	27		27				No change					
43	-11		- 3	-11		-11	14						4		
44	10	10	10	7	7	7	13	9		9			9	10	
45	26		25	-69		-60				No change					
46	25	- 3	25	11	11	11				No change					
47	- 5		-18	-60		-180									
48	0		3	11		19									
49	18		51	-150		-131									
50	60	60	60	14	14	14				No change					
51		0	0		-39	-39				No change					
52		21	21		-150	-150		No change							
53		-11	0		-66	-66		No change							
54		- 3	- 3		21	21		No change							
55		37	46		11	11	7						5		
56		24	7		11	11	14	12	3				10	10	4
57		52	0		90	90		8						9	
58	- 7		- 7	76		60			4						3
59	60		57	60		60		No change							
60	-44		-42	30		30		No change							
61	38		6	-150		-150	16	19					11	10	
62	-60		-60	101		101		No change							
63	-13		-13	0		0	2							3	
64	0		0	71		71		No change							
65	0		0	7		7		No change							
66	14		14	109		109		No change							
67	18		18	136		136		No change							

TABLE II—CONT'D

CASE NO.	DEGREE OF ANGLE OF ELECTRICAL AXIS (ANGLE ALPHA)						LEAD IV IN 0.1 MV.								
	QRS			T-WAVE			LYING			SITTING			STANDING		
	LYING	SITTING	STANDING	LYING	SITTING	STANDING	Q	R	T	Q	R	T	Q	R	T
68	39	27	37	16	16	16			8			5			8
69	-11	-11	-11	81	81	81		No change							
70	60	30	0	30	41	44		No change							
71	138	90	99	0	0	0		8	-5		10	-4		8	-3
72	13		- 8	-16		19	7								
73	-125		-125	-11		-11		No change					10		
74	-53		-60	-104		-127									
75	- 2		0	21		19									
76	-18		-18	-16		-16									
77	0		44	-30		-60									
78	101		104	-67		49		No change							
79	66		60	-139		-139	6	8-9					4-4½	5-6	
80	101		101	37		37		No change							
81	90	90	90	0	0	0		20			17			15	
82	138	138	138	90	90	90		No change							
83	65		71	11		30									
84	69		77	53		60									
85	60		69	39		19									
86	98		98	71		65									
87	40	14	9	41	22	-27									
88	22	9	0	-19	0	0									
89	- 7		15	37		37	6	5					3	8	
90	90		86	71		71		18-19	5					29	8
91	14		18	19		23		No change							
92	23		20	16		14		No change							
93	30		30	34		34		No change							
94	37		37	30		30	15	9	-10				12	12	-8
95	-30		-30	11		11		No change							
96	30	19	- 8	16	14	14	15	6		13	5		16	3	
97	60		97	-11		0									
98	-14		-17	30		0									
99	60		63	47		50									
100	60		60	49		0									

Katz and Robinow[5] and others found that displacement of the heart to the left may in some cases be associated with rotation of the electrical axis to the right, in others to the left and in still others with no rotation. The same was true of displacement to the right. In other words, changes in the electrical axis were not always consistent with the theory of the Einthoven equilateral triangle. In many cases there were merely changes in the voltage without axis shift.

Experimentally, Kountz, Prinzmetal, Pearson, and Koenig[6] found that the degree of displacement of the heart determined the resultant electrical axis and if the heart was rotated rather than displaced the electrical axis corresponded to the direction of rotation. They believed that electrical axis changes were due to alterations in the relationship of the septum of the heart to the long axis of the body.

It is unlikely that the same conditions occur in clinical cases. It is possible that in individuals with hearts of unequal size alterations in the body posture may result in unequal displacement of the heart. Given a group of similar cases, as in our series such a condition is not likely to occur. Furthermore it is not conceivable that alterations of body posture from sitting to standing would change the anatomical axis of the heart to a sufficient degree to affect the electrical vectors. The explanation of such changes cannot therefore be made on the basis of change of the position of the heart.

An explanation of these changes is to be had perhaps in the work of Katz and his coworkers. Katz and Korey[7] insulated various areas of the heart in dogs and found that the lungs and large systemic vessels were poor conductors of the electric current elaborated in the heart while the solid structures in contact with the heart were good conductors. They felt that changes in the electrocardiogram with alterations of posture were due largely to reorientation of various parts of the heart with good and poor conductors which alter the current coming from the heart. In other words they believed that not all portions of the heart share equally in giving rise to an electric vector, and that the changes in the electric field with alterations of posture are not due to reorientation in the three dimensions of the resultant vector. It is the contact of various parts of the heart with different adjacent conducting media that determines the resultant electrocardiogram. "Electrical axis" or "shift in the electrical axis" are misnomers, according to their conception. They considered the area of cardiac dullness, the diaphragm and the lower part of the posterior muscle mass of the vertebral column to be good conductors. Later, Katz and his associates[8] further demonstrated the importance of the electrical properties of the tissues adjacent to the heart in determining the type of electrical current set up in the heart.

These experimental observations would explain not only the changes in the electrocardiogram with alterations of posture from reclining to

standing but also the changes observed on alteration of posture from the upright sitting to standing, in which cases the electrical vectors, according to the Einthoven triangle, should be the same. Slight displacement of the abdominal contents and changes in the position of the body structures in the two postures would conceivably alter the conducting media adjacent to the heart and therefore the resultant electrocardiogram.

The changes in the appearance of the T-wave independent of the QRS complex are due to differences in the mode of spread and retreat of the current. According to Lewis[9] the spread of excitation is rapid and is controlled mainly by the Purkinje system, while the period of activation, comprising the full excitatory state and recovery, is much longer and concerns the mass of ventricular muscle. Changes in the relationship of the various portions of the ventricular muscle with the adjacent conducting structures may conceivably result in changed registration of the electromotive force, incident to activation and retreat in the localized portions of the muscle.

From the observations and considerations presented in this paper it is readily seen that changes in the appearance of the T-wave with alteration of posture from standing to recumbent do not indicate latent or inactive cardiac disease as claimed by Leimdörfer.[1] On the contrary, in the interpretation of any electrocardiogram it is very important to know the position in which it was obtained before any significance may be attached to its complexes, especially to the T-waves. This is particularly true when two electrocardiograms of the same patient are compared to ascertain if any changes have occurred in the heart muscle. Unless we are sure that the tracings were obtained in identically similar postures, any changes observed may be considered due to change in posture rather than to changes in the myocardial state.

Although the number of cases in this series is not great enough from which to draw conclusions, it appears that in the normal heart there is a greater tendency to a shift of the electrical axis of the QRS complex to the right and of the T-wave to the left on change in posture from the recumbent to the standing. In abnormal hearts, the shifts are in the opposite directions. This might prove to be of help in differentiating the normal from the abnormal heart. It does not indicate, however, disease of the heart muscle, but most likely disproportion in the sizes of the right and left ventricles in the two types of hearts, with the resultant differences in the reorientation of the two chambers to their environment caused by alteration of posture.

SUMMARY AND CONCLUSIONS

Electrocardiographic studies were carried out on 100 cases on alteration of posture from the dorsal recumbent to standing and sitting positions. The three conventional leads and the fourth lead were used.

Definite changes in the appearance of the QRS and the T-waves were observed in many cases on these alterations of posture. The changes in the T-wave usually occurred independently or were different than those expected from the preceding QRS complexes. In some cases the changes were so marked as to make the electrocardiogram appear abnormal and to lose its identity with those taken in the other postures. The changes occurred as frequently in normal as in diseased hearts. In normal hearts there was a greater tendency for the electrical axis of the QRS complex to shift to the right and of the T-wave to the left, while in the diseased heart the tendency was of shifting to the left for the QRS and to the right for the T-wave. This fact might prove to be of help in differentiating the normal from the diseased heart. It does not indicate, however, disease of the heart muscle but probably a disproportion in the sizes of the left and right ventricles in the two types of hearts with the resultant differences in reorientation of the two chambers to their changed environment caused by alteration of posture from recumbency to standing.

In most cases the changes did not conform to the theory of the Einthoven equilateral triangle for the shift in the electrical axis was not always as predicted from the supposed shift of the anatomical axis. The phenomenon may be explained on the theory that there occurs a change in contact of the adjacent conducting media with different portions of the heart on alteration of body posture, producing variation in conduction.

The observations demonstrate the importance of knowing the posture in which a tracing was taken before any pathological significance is applied to it. They also may prove to be of value in determining the relative sizes of the chambers of the heart.

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THE USE OF SODIUM NITRITE FOR TESTING THE FLEXIBILITY OF THE PERIPHERAL VASCULAR BED*

WILLIAM C. BECK, M.D., AND GÉZA DE TAKÁTS, M.D.
CHICAGO, ILL.

IN THE study of the different types and stages of peripheral vascular disease, an important problem arises from the standpoint of prognosis and therapy namely: how much of the terminal vascular bed is closed by spasm or by organic disease? The production of fever with typhoid vaccine, the raising of body temperature by heat or by preventing heat loss, the application of direct heat to the affected limb, and the release of vasomotor control by peripheral nerve block or by spinal anesthesia have been extensively used to determine the patency of the terminal vascular bed. Their use has in the main been to select cases suitable for sympathectomy; and the rise in skin temperatures obtained was interpreted as a release of local, central, or reflectoric vascular spasm.

It seems more logical, however, as was first suggested by Shaw[1] to regard these tests as indicators of the reserve capacity of the vascular bed. It is true that this capacity may be diminished by vasospastic phenomena of Raynaud's or Buerger's disease, but frequently parts of the terminal vascular bed are obliterated by organic processes and the vasodilatation following any of these procedures simply indicates the residual reserve, one which is not called into play in the resting stage but functions during activity. The estimation of this collateral reserve thus becomes an important diagnostic and prognostic measure, not only in regard to the feasibility of a sympathectomy but as an aid in determining whether conservative devices, such as suction and pressure[2] or intermittent venous hyperemia,[3] offer any reasonable possibility for improvement.

THE TEST

An oscillometric curve is determined at the ankle or the wrist. A Pachon oscillometer is sufficient for the purpose but for an easier demonstration of the test we are showing records obtained with a self-registering device. In these determinations a single cuff was used. The patient lies in a horizontal position with the extremity exposed to its root. The room temperature is preferably between 70° and 80° F., although the action of sodium nitrite on the peripheral vessels is independent of environmental temperature. One cubic centimeter of a 4 per cent solution of sodium nitrite (0.04 gm.) is given intravenously at a slow rate of speed. The solution must be either prepared immediately before use or put up in dark ampules filled close to the top in order to prevent oxidation of the solution, which rapidly takes place

*From the Neurocirculatory Clinic, Department of Surgery, University of Illinois, College of Medicine. Aided by a grant for graduate research of the University of Illinois.

in the presence of oxygen.* The maximal vasodilatation occurs between ten and fifteen minutes after the injection, although the effect lasts at least for one hour (Fig. 1). After a great many tests, we take the second reading ten minutes after the injection and compare the two oscillometric curves. The patient may then get up and leave.

With this dosage we have not observed untoward symptoms in a single instance, although more than 100 patients have been subjected to this test.

THE MECHANISM OF ACTION

Sodium nitrite has been used for many years for the reduction of blood pressure, accomplished by changes in peripheral circulation. A searching inquiry as to the exact localization of vascular relaxation has been made recently by Soma Weiss and his coworkers.[4, 5, 6] They have come to the conclusion that the drug acts by decreasing the tone of the venocapillary bed, thereby producing a pooling of blood on the venous side of the circulation, which can be accentuated by assuming upright posture. These authors also state that the arterioles are not dilated, in fact, there occurs an arteriolar constriction as a response to the falling blood pressure. Blood flow is thus decreased, but the capacity of the vascular bed to hold blood must be larger. The arterioles maintain their tone and are susceptible to reflex vasomotor responses during the action of sodium nitrite.

As will be shown in some of our graphs, the marked increase in oscillometric curves may be present with practically no change in systolic and diastolic blood pressure, which can only be explained by a persistent tonus of the arterioles. It must be remembered though that our dose is much smaller and yet the action of the drug is more rapid because of the intravenous administration. Weiss and his associates used three to four times as much sodium nitrite orally. The circulatory collapse induced by them would call for an arteriolar constriction. What we seem to measure then, with our larger spikes and with the shift of our oscillometric curves to the right, is an increased filling of the venocapillary bed and a decrease in resistance in that area. As this filling is dependent on the patency of the small arteries and arterioles, we feel that the rapidity with which the venous pool forms still remains an index of arterial flow, provided the dose is so selected that a marked fall in blood pressure does not occur. When that occurs, the secondary arteriolar constriction will so cut down blood flow that the individual pulse volumes diminish and the test does not inform us as to the reserve capacity of the vascular bed. It is for this reason that the selection of the small dose of 0.04 gm. (⅔ of a grain) is important. That arteriolar dilatation can be induced by nitrites is shown by the initial flushing of the head and face, which occurs after the inhalation of amyl nitrite.† It seems to us then, that for a proper evaluation of the capacity of the peripheral vascular bed, such measures must be selected which avoid a fall in blood pressure. Even so, the element of reflex vasoconstriction to maintain this blood pressure will have to be considered.

OBSERVATIONS

We have introduced this test in our neurocirculatory clinic as a routine measure and have taken several hundred readings. We wish only to

*We gratefully acknowledge the help of Dr. Wm. C. Welker, Professor of Physiological Chemistry of the University of Illinois, in the preparation of a stable solution, which does not contain nitrates after a few weeks in the ampules. To obtain uniform results, however, it is better to dissolve the powder in a few cubic centimeters of normal salt solution and boil it in a spoon just before use.

†The temperature of cutaneous flares, produced by intradermal injections of histamine, can be raised by the intravenous administration of sodium nitrite. It is difficult to explain this finding without assuming that arteriolar dilatation has taken place.

show a few graphs to illustrate the value of the drug and to compare it with other known methods employed to produce vasodilatation.

Figure 1 illustrates the effect of the drug in a normal, young individual. It will be noted that the effect is at its peak at ten and fifteen

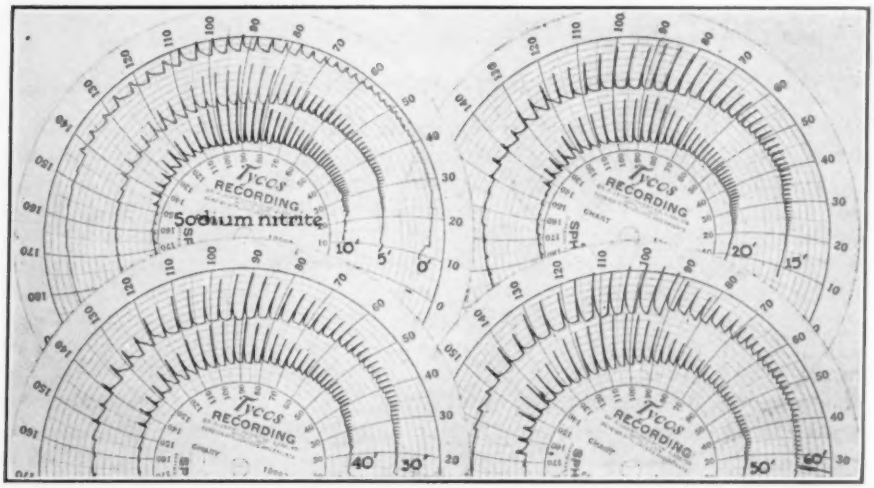

Fig. 1.—Oscillometric records in a young individual with normal circulation. The measurements in this and the following graphs were made with a single cuff at the ankle. Following a reading obtained at zero, 1 c.c. of a 4 per cent solution of freshly prepared sodium nitrite solution was injected. Note the greatly enlarged pulse volumes. The shift of these spikes toward the right half of the chart indicates a lowering of peripheral resistance. It is most marked at fifteen minutes, where the spikes between 80 and 70 millimeters of mercury are the largest. The effect is still present at the end of one hour.

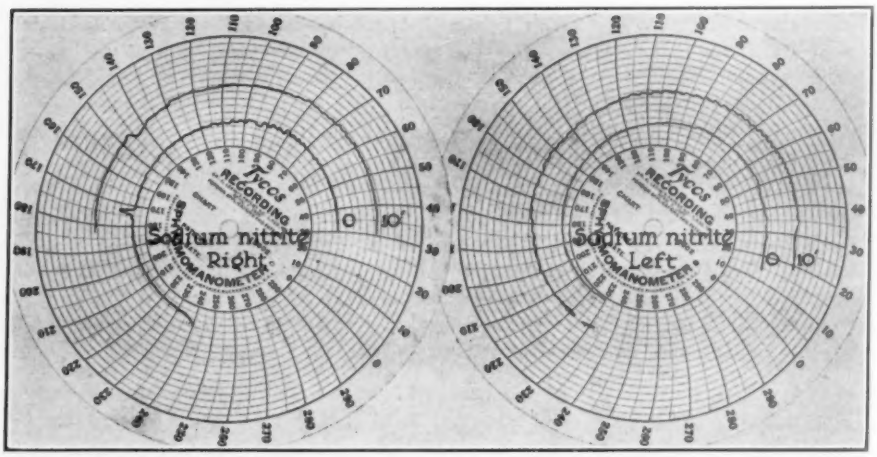

Fig. 2.—A fifty-six-year-old male with obliterating arteriosclerosis of both lower extremities. Oscillometric curves before and ten minutes after sodium nitrite was given. There is a slight shift of the oscillations to the right. Curiously enough, the left side, which showed less oscillations than the right, gave a better response to the drug.

minutes, but that it is still present at the end of one hour. In this it differs from amyl nitrite, which acts very abruptly and produces a sudden fall in blood pressure, the maximum fall being caught usually

between thirty and forty-five seconds after inhalation. Although we used amyl nitrite in a few of our hypertensive patients to demonstrate the flexibility of the diastolic level, we have now abandoned its use because of the disagreeable and perhaps not entirely harmless symptoms.

In obliterating arteriosclerosis the flat or absent oscillometric curve is hardly influenced by the intravenous administration of sodium nitrite (Fig. 2). The same is true in thromboangiitis obliterans with extensive

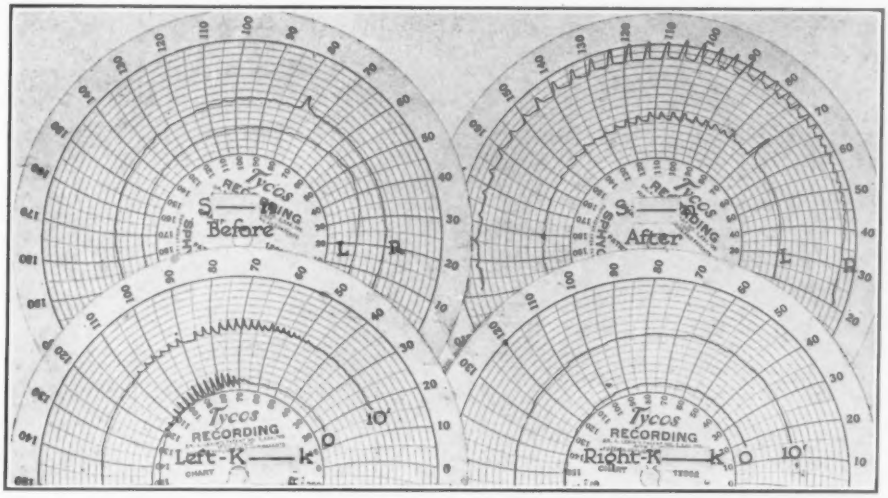

Fig. 3.—Two patients suffering from Buerger's disease. In the case of Sn., the left lower extremity shows much smaller vascular capacity than the right. In the case of Kk., the right lower extremity did not respond at all. Both patients showed a far greater clinical improvement after sympathectomy on the side which responded better to sodium nitrite.

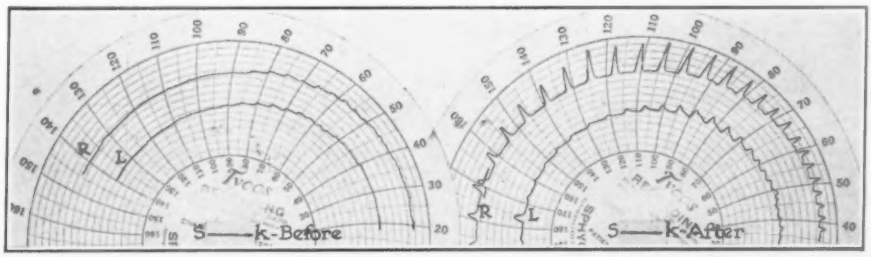

Fig. 4.—A twenty-three-year-old student, showing a marked difference in response to sodium nitrite. Clinical diagnosis was Buerger's disease, with impalpable pedal arteries of both feet. Following sodium nitrite both vessels of the right foot became palpable. The vasospasm in the right foot is here clearly demonstrated. The left lower extremity is in a more advanced stage of the disease.

organic damage in the absence of superimposed spasm. In the earlier cases of Buerger's disease, however, the response may be marked (Fig. 3). When both lower extremities, or all four extremities are involved, the test may give evidence of different grades of involvement (Fig. 4). We have come to rely with increasing assurance on this test in regard to the benefit to be derived from a sympathectomy. The extremity with a

poor response to sodium nitrite will not react as favorably as the one with a good response. This does not mean that the lack of good response contraindicates sympathectomy. The benefits of this operation in Buerger's disease have been discussed by one of us elsewhere,[7] but the

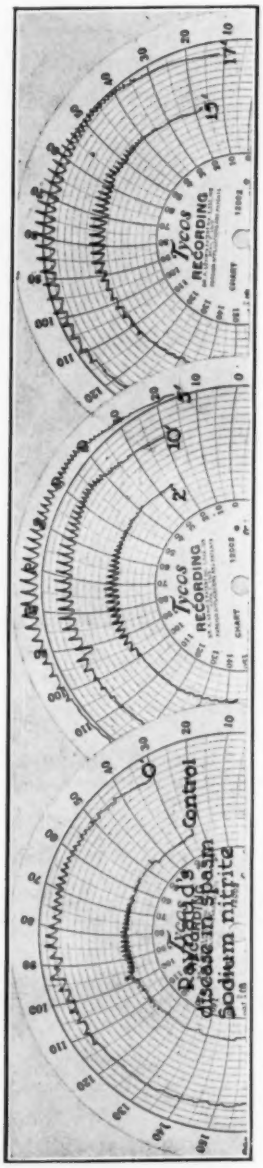

Fig. 5.—A. M., A thirty-one-year-old woman suffering from Raynaud's disease. The first reading was obtained during spasm as a control curve. At zero, the needle was inserted. The last reading at seventeen minutes seemed to give the maximum response. The pallor and cyanosis of the fingers disappeared at ten minutes. The test demonstrates the lack of marked structural change in the terminal vascular bed. She was subjected to sympathectomy.

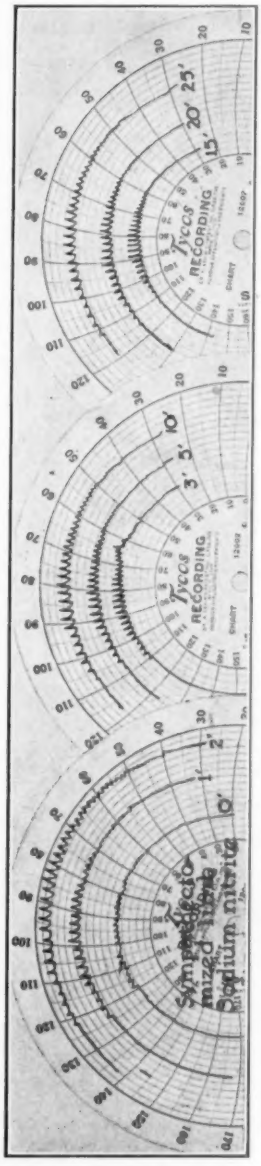

Fig. 6.—A forty-five-year-old male in whom preganglionic thoracic sympathectomy was performed three months previously for a persistent chronic ulceration due presumably to a defect in the spinal cord. Good response of the sympathectomized vessel. Oscillations diminish after ten minutes.

test gives a good indication as to what may be expected. In Raynaud's disease, the presence or absence of structural damage can be demonstrated by this test. Thus in Fig. 5 it was possible to release a vasospastic attack by nitrite and show that the opening of the minute vessels is readily accomplished in this case.

Sympathectomized or completely denervated extremities show normal response to this test (Fig. 6). Following exposure to heat, sodium nitrite gives evidence of a further increase in capacity (Fig. 7). Compared with papaverine, sodium nitrite acts much more rapidly, although the action of papaverine is more prolonged. At ten minutes the action of sodium nitrite compares favorably with the action of papaverine at thirty minutes (Fig. 8).

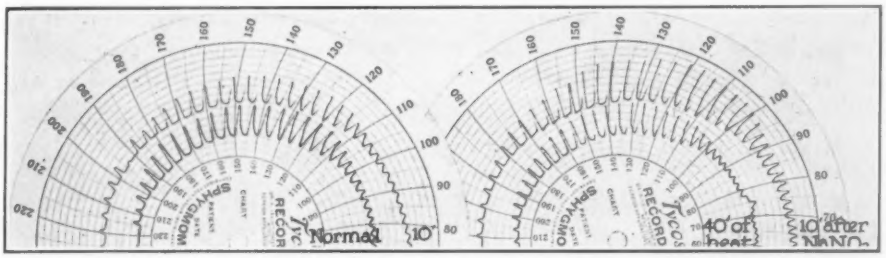

Fig. 7.—The response of a preheated extremity to sodium nitrite. After forty minutes of direct heat at 110° in a thermostatically controlled cradle, vasodilatation is still possible with the use of sodium nitrite.

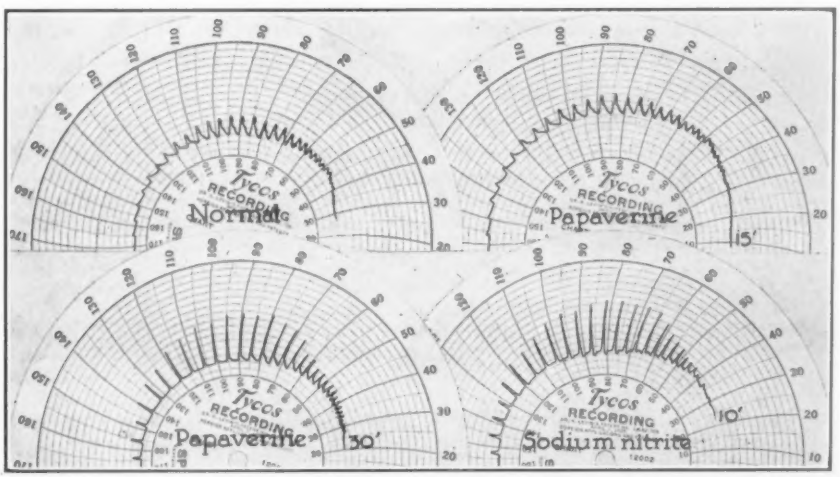

Fig. 8.—Comparative effect of sodium nitrite and papaverine. The maximum vasodilatation after the intravenous use of papaverine was attained at thirty minutes. A corresponding effect could be obtained in ten minutes with sodium nitrite. At fifteen minutes, papaverine has hardly started to act.

DISCUSSION

With a simple and, as far as our experience goes, quite harmless test, it is possible to obtain a graphic picture of the capacity of the peripheral vascular bed. This capacity will naturally depend on the age of the patient, on environmental temperature, metabolic requirements, and amount of spasm, but chiefly on organic vascular damage involving the terminal vascular bed. Thus we believe that it has prognostic value, as the chances of reopening the terminal bed are notoriously poor, and it is

in this group, as Herrmann and Reid have pointed out, that suction and pressure treatments are least effective.[2]

The graphs indicate that peripheral vasodilatation may be readily induced with a small amount of sodium nitrite without producing a significant fall in blood pressure. Whether the drug acts primarily on the veno-capillary bed or, as we believe, produces a diffuse relaxation of the terminal bed with secondary arteriolar constriction in order to maintain blood pressure does not affect the usefulness of this method. Obviously if the dose is so selected that larger drops of blood pressure are avoided, the diminution of blood flow, as a consequence of reflectoric arteriolar constriction, will not be a disturbing factor. The dose is so selected that even patients with marked hypertension will not experience a significant fall in blood pressure.

SUMMARY

For a test of the capacity of the terminal vascular bed, a simple ambulatory test is described. It consists of a preliminary determination of an oscillometric curve, followed by the intravenous administration of 0.04 gm. (⅔ grain) of freshly dissolved sodium nitrite solution. From ten to fifteen minutes later a second oscillometric curve is determined. The comparison of the two curves as to the height of oscillations and the shift of the spikes toward lower levels of pressure give a graphic illustration of peripheral vascular capacity.

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THE ELECTROGRAM OF CARDIAC MUSCLE: AN ANALYSIS WHICH EXPLAINS THE REGRESSION OR T DEFLECTION

A. Garrard Macleod, M.D.
New York, N. Y.

I

EVER since the discovery that an electrical response is associated with the activity of certain tissues, physiologists have been interested in ascertaining the origin and nature of these currents. While these two subjects are closely associated, they are not identical. In the former belongs the effort to discover the physicochemical reactions in tissue that produce the electrical energy, in the latter, the endeavor to ascertain the character of the currents produced, their distribution and association with the other manifestations of activity. To the general physiologist the origin of the electrical response has been the subject of greater interest while the nature of the currents has been investigated only as a means to this end. But now that electrocardiography has come to play an important rôle in clinical medicine, a clear description of the electrical events which take place in a single cardiac muscle fiber as a result of activation is a matter of practical importance apart from any light it may throw upon the origin of these currents. Since this investigation sheds no direct light on the origin of action currents the history of that subject will not be discussed. Meanwhile it is desirable to consider briefly the state of knowledge of their nature—at least so far as heart muscle is concerned.

The experiments upon which this knowledge is based fall into two categories, those performed in moist air and those in which the tissue is in situ or is immersed in a vessel containing physiological salt solution which serves as an extensive conducting medium. However the experiments were performed, provided only that the muscle was uninjured, the response obtained consisted of two parts, a rapid primary deflection and a slower secondary or T deflection.

In the first group of experiments it was invariably found that when one electrode connected with a galvanometer was on active and the other on resting muscle, the active muscle was negative with respect to the resting. Consequently, the first theory to gain general credence was the so-called negativity hypothesis or theory of distributed potential differences. According to this theory active muscle becomes negatively charged (Fig. 1*A*). While anyone familiar with electrical phenomena

From the Hospital of the Rockefeller Institute for Medical Research, New York.
A preliminary report of this work was read before the American Society for Clinical Investigation in May, 1935.

from the physical point of view would have found many reasons for considering the theory untenable, it explained fairly satisfactorily the early experiments performed on simple muscle strips suspended in moist air.

It was not until Lewis[1] began his investigations of the electrocardiogram that this theory was seriously questioned. After making a critical study of the spread of the impulse over the heart with the organ in situ he discovered that he could not explain his observations on the assumption that all active muscle was negative relative to resting, for he found that the sign of the galvanometric deflection depended only upon the direction in which the impulse was at the moment spreading and not on the location of the mass of active muscle as a whole with respect to the mass of resting muscle. He put forward an hypothesis, therefore, which he called the theory of limited potential differences. The view was that only the muscle which had just become active was relatively negative and that only the inactive muscle immediately adjacent was relatively positive (Fig. 1*B*). This idea adequately explained all his experimental observations. Lewis did not push the idea beyond his immediate needs, however, and did not make use of it in his explanation of the secondary or T deflection. It is unwise to conclude what an author's view would have been about a situation which he did not discuss unless such a view follows unequivocally from definite statements in his published work. No effort is made, therefore, to carry Lewis's theory further than he himself carried it. For a time there seems to have been little interest in the subject. But in 1927, Craib,[2] working with cold-blooded and mammalian hearts immersed in large baths of physiological saline solution, made an accurate study of the electrical field surrounding active heart muscle, and demonstrated, though not for the first time, the necessity of applying the laws which govern the distribution of potential in volume conductors* to this problem. Because he found while making these studies that he could assume the source of potential difference during systole to be a doublet† he proposed a doublet theory for the nature of the electrical manifestation of muscular activity. According to this theory, at the moment of activation,

*By a volume conductor is meant an extensive tridimensional conducting medium. A jar of physiological saline solution, or the body of a patient or an animal is a conductor of this sort. Certain of the early investigators, notably Waller and Einthoven, understood that it was necessary to apply the laws which govern the distribution of potential in volume conductors when dealing with the heart in situ, and whatever simplifying assumptions they made they were careful to justify. Later investigators for the most part, however, did not realize the necessity of the application of these laws. The report of Wilson, Wishart, and Herrmann[6] in 1926 was probably the first in more recent years to call attention to the fact that the body must be regarded as a volume conductor.

†A doublet is a positive and negative pole of equal strength located very close together, strictly speaking infinitely close together, i.e., a potential difference with magnitude and direction located at a point. The conception is a mathematical fiction devised to facilitate the application of mathematics to the solution of electrical problems. A potential difference which extends over a very small space behaves, of course, under certain circumstances, like a doublet; any potential difference can be represented by a combination of doublets. Craib may not have appreciated the fictitious character of doublets and the equivalence of a train of doublets to a potential difference extending over a space.

doublets develop in the tissue and endure there for a brief period. Later, as activity subsides, doublets of opposite sign appear and last a somewhat longer time (Fig. 1*C*). Results of experiments on muscle strips could be accurately predicted from this theory whereas predictions on the basis of the old negativity hypothesis could not be verified.

Finally, Wilson, Macleod, and Barker[3, 4] made an extensive study of the laws which govern the distribution of potential in volume conductors and their application to the problems of electrophysiology. They treated the subject more generally than Craib had done and reduced their analyses to mathematical form. In this way they were able to plot curves that should be obtained if the conditions assumed prevailed and to compare these with electrograms obtained by experiment. There was very close agreement between their theoretical and their actual curve. Their conclusion was, "whatever may be the origin of the elec-

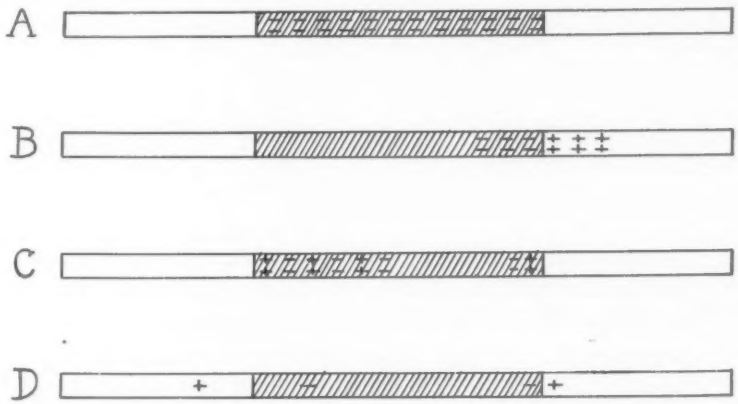

Fig. 1.—A diagrammatic representation is given of the various theories of the nature of the electrical manifestations of activity in cardiac muscle. In each case activity is spreading from left to right. The active region is shaded.

A. The negativity hypothesis. The entire mass of active muscle is represented as being negatively charged. The inactive muscle is neutral.

B. The theory of limited potential differences (Lewis). A small region where the muscle has just become active is negative and the immediately adjacent resting muscle is positive.

C. The doublet theory (Craib). As muscle becomes active it becomes the seat of doublets whose positive element is toward the resting muscle. When muscle regresses from the active state, it gives rise to doublets of opposite polarity.

D. Bipolar theory (Wilson, Macleod, Barker). Ahead of the advancing boundary between resting and active muscle is a positive pole and behind it a negative pole. Across the retreating boundary is a potential difference of reversed polarity but in this case the poles are farther apart.

tric currents associated with the excitation wave, these currents are similar to those which would be produced if the crest of the excitation wave were immediately preceded by a source (positive pole) and followed by a sink (negative pole)." They suggested also that the secondary or T process is caused by a sink followed by a source, but that in this case the poles are farther apart (Fig. 1*D*).

The first (negativity) theory in the light of present knowledge is untenable. The difficulties with it have been pointed out by Craib[2] and

by Wilson, Macleod, and Barker[3] and need not be dealt with at length, except to point out the nature of the fallacy involved. If a strip of muscle *AD* (Fig. 2) surrounded by moist air is stimulated at *A*, its active (shaded) portion is negative with respect to its resting portion. In other words, so long as the boundary between active and resting muscle (*X*) is between *B* and *C*, an electrode at *B* is negative with respect to one at *C*. The inference drawn was that this result signified that active muscle was negatively charged because inactive muscle was neutral (Fig. 1*A*). This, however, is only one of two possible explanations. An equally satisfactory and more probable one is that a potential difference exists at the boundary *X* between active and resting muscle (Fig. 1*D* as contrasted with Fig. 1*A*). Under the circumstances just described, with the muscle suspended in moist air, if a potential difference existed at *X*, the strip *BX* would act as an extension of the electrode *B* and, therefore, seem to be negative, and *XC* as an extension of *C*, and seem positive. In the case of a linear conductor, which a mus-

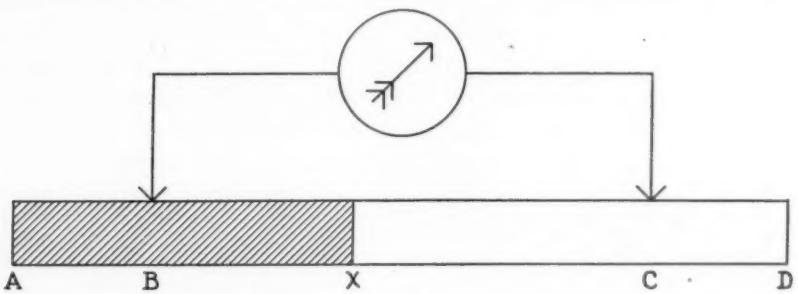

Fig. 2.

cle strip suspended in air closely approximates, it is impossible to differentiate between the two explanations. If the muscle strip were immersed in a sufficiently large bath of saline solution, however, it could be ascertained which explanation is correct, that is, whether the entire mass of active muscle behaves as an extensive negative pole and the entire mass of resting muscle as an extensive positive pole, or whether there seems to be a localized positive and negative pole close together in the region of transition *X*. The propounders of the last three theories (Fig. 1, *B, C, D*) have done such experiments and have found the second situation to represent the facts. The three are not dissimilar. Each may in a sense be regarded as an extension and clarification of the preceding.

Lewis explained that his theory of limited potential difference was vague. Nevertheless he demonstrated that the excitation wave is preceded by a positive and followed by a negative region, and that both are of small extent. His failure to offer an explanation of the secondary or T deflection in terms of his theory was its greatest omission.

Craib's doublet theory explained consistently both QRS and T, but was purely qualitative and predicted little more than the sign of the deflections. In the case of the secondary (T) deflection his predictions were furthermore not well borne out by the experimental curves.

Wilson, Macleod, and Barker were more precise in their concepts, and their deductions were expressed in mathematical form so that they were able to predict the shape of the primary deflection with considerable nicety and to demonstrate the significance of the various inflections of the curve. This made it possible to ascertain from the recorded curve a fairly precise description of the electrical process which produced it. They did not attempt to predict the form of the T-wave in direct leads but were able to show by an indirect method that it bore a quantitative relationship to the QRS deflection and was produced by electrical forces of opposite sign.[4, 5] In a different way each theory has demonstrated that as the excitation wave spreads, it is accompanied by a positive and a negative region each of limited dimensions. The way in which each has pictured the behavior of the electric forces is different, but the differences are superficial, and all are in agreement as to the fundamental nature of the process. Both Craib, and Wilson, Macleod, and Barker have indicated that the secondary or T deflection is probably produced by forces of opposite sign to those that cause the QRS, and that it has to do with the recovery from the active states. But the nature of this process is still far from clear. The object of this research is to describe intimately the concepts of activity in general and the electric phenomena which accompany it, to relate the one to the other and thereby to explain more satisfactorily the nature of the secondary (T) deflection.*

II

This investigation deals primarily with an explanation of the secondary or T deflection. But since it makes use of a new method of analysis, it seems best for the sake of clarity, to deal briefly with the electrical process as a whole.

The ideal experiment for a study of this kind is one in which the physical circumstances are sufficiently well understood and sufficiently simple so that potential changes occurring in a given segment of active tissue can be easily and unequivocally inferred from the record obtained. As has been mentioned, certain information can be gained from experiments in which appropriate tissue is immersed in an extensive conductor

*The work of Eyster, Maresh, and Krasno (Am. J. Physiol. **110**: 422, 1934) and Krasno, Eyster, and Maaske (Ibid. **114**: 119, 1935) has not been discussed in this paper because their work deals with the potential changes in the heart as a whole as judged by indirect leads rather than the electrical events occurring in a single fiber. These authors have made use of a doublet concept but the doublets which they assume are the resultants of all the potential differences existing anywhere in the heart at a given moment. Theirs clearly is a different concept from the one used here where doublets are used to explain the potential differences existing in single music fibers. For these reasons the work of the authors mentioned requires no detailed analysis and comparison with the discussion in this paper. This excellent work will be reviewed in a more appropriate connection.

(a saline bath) that is not forthcoming from experiments performed with preparations suspended in air. There is a distinct disadvantage, furthermore, in placing both electrodes on the tissue being studied, since it is then impossible to tell whether a given deflection is produced by a positive effect at one electrode or a negative effect at the other. As Wilson, Macleod, and Barker[3] showed, this difficulty can be avoided by placing one electrode, the exploring electrode, on the tissue under observation, and the other, the indifferent electrode, in the conducting medium at a sufficient distance from the first so that potential differences arising in the active tissue will produce undetectable, because so small, changes in potential in it. The record then describes the potential changes occurring at the point in the active tissue upon which the exploring electrode has been placed. It is, in addition, necessary to know the configuration of the muscle and the way in which the active process passes over it. While a long narrow strip of tissue in which impulses spread from one end to the other would be ideal, it is not practicable to cut such a strip from the heart since it is especially necessary to avoid the complication of electrical effects attributable to injury.

In the auricle of the Louisiana bullfrog, *Rana catesbiana*, the impulse spreads in such a way that the conditions on its anterior surface approximate those in a simple strip of muscle. The impulse arises in the sinus venosus (Fig. 3A, *SV*) and spreads in the auricle from *A* toward *B*. If this anterior portion of the auricle were flattened out its shape would resemble Fig. 3B. At a given moment the division between active and resting muscle might occupy the position of the dotted line. The point *X* indicates the position of the exploring electrode. This arrangement approximates the situation which Wilson, Macleod, and Barker designate as "parallel excitation"[3] (Fig. 3C). They have shown that the electrogram under these circumstances differs only quantitatively from one produced in a narrow strip.

The impulse arising in *SV* spreads to the ventricle also over the posterior auricular wall on the dorsal aspect of the heart. The potentials produced in this bit of muscle are small and sufficiently distant from the exploring electrode so that their effect is negligible.

In performing an experiment the animal was first pithed to prevent muscular twitching. The chest and pericardium were then opened and in some experiments heart-block was produced by pulling tight a ligature laid around the A-V groove. Since it was necessary to approximate the conditions of an extensive uniform conductor, good contact with all the surrounding tissues was maintained by filling the body cavity with saline solution when necessary. At the site where the exploring electrode was to be placed a small patch of the epicardium was dissected off without injuring the underlying muscle. A small exudation of fibrin then caused the electrode, which consisted of a piece of

thread protruding from the end of a silver tube, to adhere to the muscle without slipping during contraction. The indifferent electrode, a strip of silver, was placed beneath the skin of the hind leg.

Since the resistance of the exploring electrode was of necessity high, a single stage direct current amplifier was used in conjunction with the string galvanometer. The maximum gain of this amplifier was approximately 10. It had, however, to be stable and more than usually "quiet" because of the extreme sensitivity of the recording instrument. The sensitivities actually employed were deflections of 1 to 2 cm. per millivolt. Figure 3A is a diagram of the arrangement in a typical experiment.

When the exploring electrode was placed midway between *A* and *B* (Fig. 3A) the curve obtained was like the recorded curve of Fig. 10C. It may be considered to consist of two parts, a primary deflection which is rapid and diphasic (positive-negative) and a secondary deflection

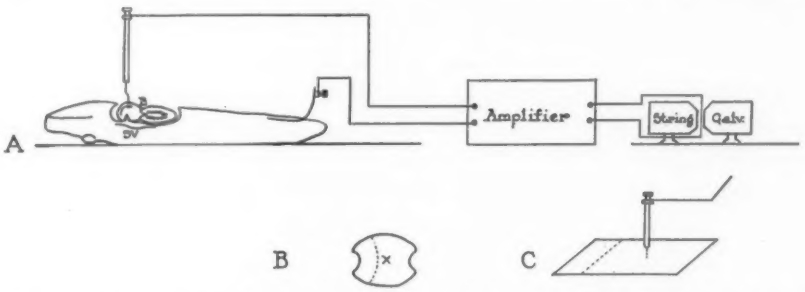

Fig. 3.—A. A schematic arrangement is shown of the method of obtaining electrograms from the uninjured auricle of the frog.
SV = sinus venosus.
A = junction of anterior wall of auricle with sinus venosus.
B = junction of anterior wall of auricle with ventricle.
B. This illustrates the approximate shape of the anterior wall of the auricle. The dotted line represents the position of junction between active and resting muscle at a given moment.
X is the position of electrode.
C. A uniform sheet of muscle is shown in which activity is spreading from left to right. The dotted line indicates the position of the boundary between resting and active muscle at a given moment. This figure illustrates what Wilson, Macleod, and Barker refer to as "parallel excitation."

which is slower and monophasic (positive). An approximately isoelectric period separates these two deflections. The rapid primary deflection of this electrogram corresponds to the QRS group of the electrocardiogram and the secondary deflection to the T-wave.

When the exploring electrode is placed near the auriculoventricular junction the curve obtained is seen in Fig. 11C. This curve differs from the preceding in that the positive phase of the primary deflection is much larger and the negative phase smaller. The portion of the curve separating the primary and secondary deflections is above the isoelectric line, and the secondary deflection is smaller. Finally, if the exploring electrode is placed nearer the sino-auricular junction, the elec-

trogram obtained (Fig. 12C) differs from the one obtained from the central region in an opposite way from the one just described. The positive phase of the primary deflection is smaller and the negative phase larger, the portion of the curve which separates primary and secondary deflections is below the isoelectric line and the secondary deflection is larger.

To explain the form of these curves it is first necessary to return to a consideration of certain theoretical matters.

III

Before considering the electrical events which take place in a muscle fiber during activity it will make for clarity if the general process of activation is described.

If a long muscle fiber (Fig. 4A) is stimulated at the left end, the excitation process spreads toward the right at a certain velocity which may be designated V_e. When it reaches each minute muscle element such as x_1, x_2 this element becomes active and remains so for a time (T) and then returns to the resting state. During the time (T) that x_1, x_2 is in some stage of activity, the excitation process will have progressed along the fiber. The distance traveled will be TV_e. At any instant after stimulation a length of muscle (L) equal to TV_e is, therefore, in some stage of activity. That is what is meant by the length of the active process. The total time during which the segment is active (T) may be divided into three parts, the period during which its activity is increasing (T_1), the period during which it is fully active (T_2), and the period during which its activity is regressing (T_3). During these intervals T_1, T_2, T_3 the excitation process will have traveled the distances $T_1 V_e$ (*AB*, Fig. 4A), $T_2 V_e$ (*BC*, Fig. 4A), and $T_3 V_e$ (*CD*, Fig. 4A). These are, respectively, the lengths of the stages of increasing, full, and decreasing activity. Consequently, that portion of a muscle which at any moment is active may be represented as consisting of three parts, a region where activity is increasing (*AB*, Fig. 4A), a region whose activity is fully developed (*BC*, Fig. 4B), and a region where activity is regressing (*CD*, Fig. 4B). During activation a tripartite process of this kind may be pictured as passing along the muscle at the velocity V_e. In the discussion which follows, therefore, the excitation process will be represented as in Fig. 4B. A knowledge of the actual values of T_1, T_2 and T_3 and V_e constitutes a fairly accurate description of the excitation process. How these are ascertained from a recorded curve will be related in a subsequent report. In this discussion, arbitrary and appropriate values have been assigned to them.

V_e as has been said is the velocity of excitation. This (velocity of excitation) is equal to the velocity of the progress of complete recovery, V_r, if T is the same for every muscle segment. In other words, the

velocity of the right end of the shaded area (Fig. 4A) is equal to the velocity of the left end. If T were to become progressively shorter, however, from left to right, V_r would be greater than V_e, for the length of the active process would be shortening as it progresses; and if T were to become progressively longer from left to right, V_r would be less than V_e, for the process would be lengthening as it progresses. If a uniform fiber is in a uniform environment, however, V_e will be uniform, T will be the same for each element, and V_e will equal V_r. It is these simple circumstances which are assumed to be present in the analyses which follow.

The electrical events accompanying activity may now be described. There is good experimental support for the belief[2, 3] that a potential difference exists at the junction between active and resting muscle, and that this potential difference is such that the positive pole is toward the resting muscle. Since active muscle must in some way differ from resting muscle, and since at the junction between any two substances that

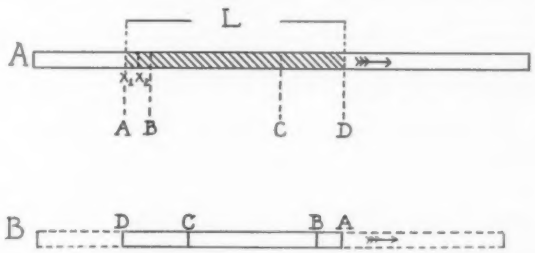

Fig. 4.—A. A muscle strip is stimulated at the left end. The shaded area represents the extent to which the excitation process spread during the time that the muscle in x_1x_2 was in some state of activity.

AB indicates the distance traveled by the front of the active process while activity was increasing in x_1x_2.

BC indicates the distance traveled by the front of the active process while activity was full in x_1x_2.

CD indicates the distance traveled by the front of the active process while activity was regressing in x_1x_2.

B. The tripartite process of activation which is traveling along a muscle strip. The muscle from *A* to *B* is increasing in activity; from *B* to *C* is fully active; and from *C* to *D* is decreasing in activity.

differ from each other chemically or physically, a potential difference may exist, it is probable that in the present case the potential difference occurs because of the difference in composition between active and resting muscle. In the sense that the transition from resting to active muscle constitutes a change in phase, the action current may be considered as resulting from a phase boundary potential. What the ionic mechanism may be, whereby this potential difference is produced, is for the present irrelevant.

A long muscle fiber has been stimulated at the left end and that portion of it which is at the moment active is shaded (Fig. 5). The depth of the shading roughly represents the degree of activity. For convenience the active portion has been divided into small equal segments.

The transition from resting to active muscle at *A* is represented as being abrupt, but that in the reverse direction, in the region *BC*, as taking place in four steps. If the assumption which has been made is correct, a potential difference exists across the boundary *A*, such that its forward looking aspect is positive and its backward looking aspect negative. Across any boundary between *A* and *B* no potential difference exists, however, for the constitution of the muscle on one side is precisely the same as on the other, both fully active. In the case of the boundary at *B*, however, the muscle to the left is slightly less active, than that to the right. Consequently, a potential difference should occur here of smaller magnitude than that at *A*, and of opposite direction. A similar situation exists at each of the segment boundaries in this region, including the one at *C*. The sum of all these potential differences must, of course, be equal in magnitude to the single one at *A*, for one transition is sim-

Fig. 5.—A diagram representing a muscle strip is shown in which the active process is progressing toward the right. The shaded area is the active portion at a given moment. The depth of the shading roughly indicates the degree of activity.

A indicates junction of resting and active muscle.

BC indicates region of decreasing activity.

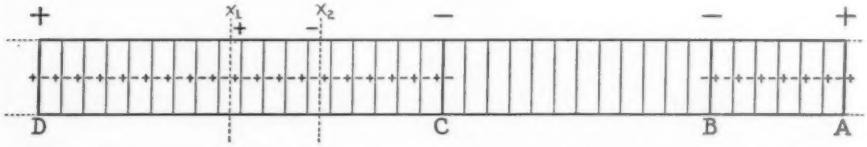

Fig. 6.—A muscle strip is shown in which the active process is progressing toward the right. The active region is divided into small segments. Each is supposed to be in a uniform state of activity throughout its extent. In the region *AB* activity is increasing and each successive segment is more active than its neighbor to the right. In the region *CD* each segment is less active than its neighbor to the right. A potential difference exists between every two adjacent segments if their states of activity are different. In the transitional regions trains of doublets thus arise. These trains are equivalent to a positive and negative pole separated by their length. The total change in potential is the same for both transitions. Thus a given length of muscle x_1x_2 contains a smaller proportion of the total if it is in the region *CD* as depicted than if it were in the region *AB*.

ply the reverse of the other. A transition from resting to active muscle, or vice versa, in reality does not occur abruptly or even in a series of distinct stages, but gradually. In other words, if the number of segments in the region *BC* were greatly increased, the facts would be more correctly represented. In this case each individual potential difference would be less, for the sum must remain the same. In similar fashion, instead of an abrupt transition at *A*, a gradual one of short duration (in many short steps) would represent the course of events more accurately.

Since the number of segments in the transitional regions may be increased without limit, thus approximating the gradual transition with

any desired degree of accuracy, and since a doublet is defined as a positive and a negative charge infinitely close together, muscle in the transitional state may be considered to be the seat of a train of doublets (Fig. 6). It is well known that such a train is equivalent, furthermore, to a single positive and a single negative pole located at either end of the train (Fig. 6). This leads to a generalization of importance, namely, that any bit of muscle, such as x_1, x_2 (Fig. 6) in the transitional state may be considered to have a positive pole located at its less active and a negative pole at its more active end.

As has been pointed out (Fig. 4B) the active process may be graphically represented as a rectangle divided into three parts corresponding to the phases of increasing activity, full activity, and decreasing activity

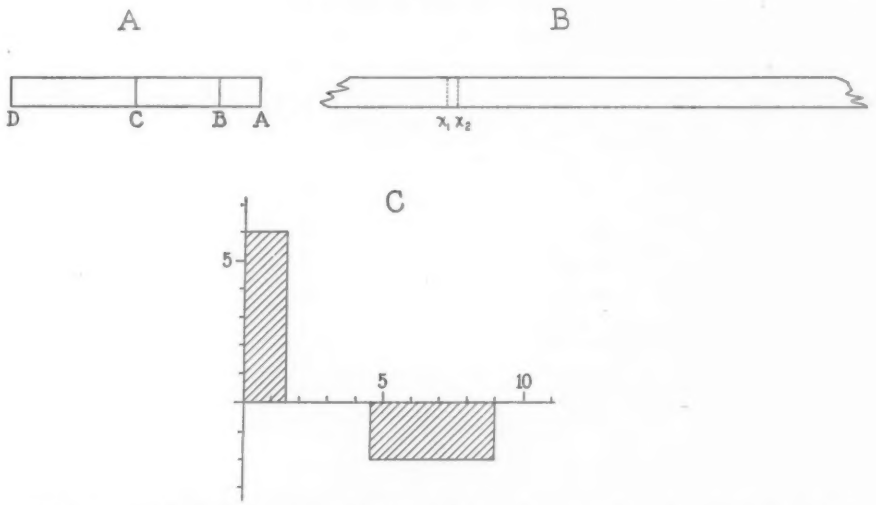

Fig. 7.—A diagram is shown indicating how the process of activation passes over a muscle strip.

A is the process of activation schematically represented.
AB is the stage of increasing activity.
BC is the stage of full activity.
CD is the stage of decreasing activity.

B. Muscle fiber over which the active process *A* is to pass. x_1x_2 is small segment of muscle whose electrical activity is plotted in *C*.

C is a graph illustrating the electrical phenomena attendant upon the activation and recovery of x_1x_2. The abscissas are arbitrary units of time and the ordinates appropriate units of potential.

(Figs. 6 and 7A). Since the same change in state, and therefore the same change in potential, is accomplished in the region *AB* as in the region *CD*, it must follow that a given short length of muscle, such as x_1, x_2 (Figs. 6 and 7B), will contain a greater proportion of the total potential difference existing between resting and active muscle when it is in a region where activity is increasing than when in a region where activity is decreasing. The magnitude of the potential difference existing in x_1, x_2 during increasing activity is, furthermore, as much greater than that during decreasing activity as *AB* is shorter than *CD*.

On the basis of this analysis it is possible to illustrate graphically the the electrical events taking place in a small segment of muscle such as x_1, x_2 during activation and recovery (Fig. 7B). While activity is increasing in the region x_1, x_2 the muscle near x_1 is more active than that near x_2 and the segment is consequently the source of a potential difference whose negative pole is at x_1 and whose positive pole is at x_2. This magnitude is plotted above the axis of abscissas and is given the arbitrary value of 6 (Fig. 7C). Its duration is equal to the duration of the phase of increasing activity. In other words, the electrical activity of x_1, x_2 during the phase of increasing activity is represented by a rectangle whose height is 6 and whose width is equal to *AB*. While the muscle throughout x_1, x_2 is fully active, no potential difference exists within these confines, so for a period equal in length to *BC* there is no quantity to be represented. But when the muscle in x_1, x_2 begins to decrease in activity, a potential difference again develops and persists for a period equal in length to *CD*. During this period the muscle in the vicinity of x_1 is less active than that in the vicinity of x_2 so that a

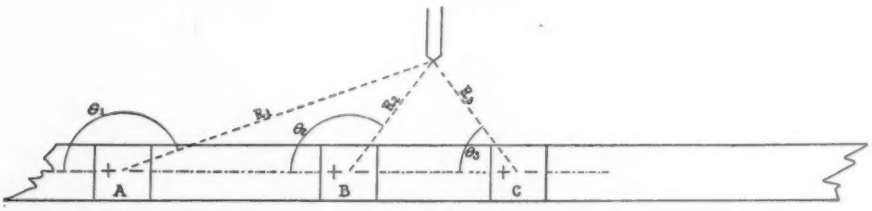

Fig. 8.—The effect is shown of variously placed doublets upon the electrode. *A* has less effect than *B* but both effects are negative. The effect of *C* is equal in magnitude to that of *B*, but positive.

positive pole will exist at x_1 and a negative one at x_2. Since the potential difference is opposite to that present during increasing activity, it is plotted below the axis of abscissas. A rectangle results, therefore, one-third as tall and three times as long as the one representing the electrical activity during the phase of increasing activity for *CD* is three times as long as *AB*. Before proceeding to the consideration of an actual experiment, another matter must be considered.

An exploring electrode is now represented in relation to the long muscle fiber (Fig. 8). For reasons previously pointed out, it is unnecessary to consider the potential changes of the indifferent electrode (the one at a distance from the active tissue). Since the muscle is immersed in an extensive conduction medium of uniform conductivity, the law[3] ($E = \frac{\mu \text{ Cos } \theta}{R^2}$) applies, where *E* is the effect upon the electrode produced by any given dipole, *R* the distance of the electrode from the center of the dipole and θ the angle between the line from the tip of the electrode to the center of the dipole and the positive end of the axis of the dipole.

This equation expresses the obvious fact that any potential difference anywhere in the medium has an effect upon the electrode, that the more distant it is the less its effect and, furthermore, that its orientation with respect to the tip of the electrode also has an effect. When the positive element is closer (Fig. 8*A*) the effect is positive; when the negative is

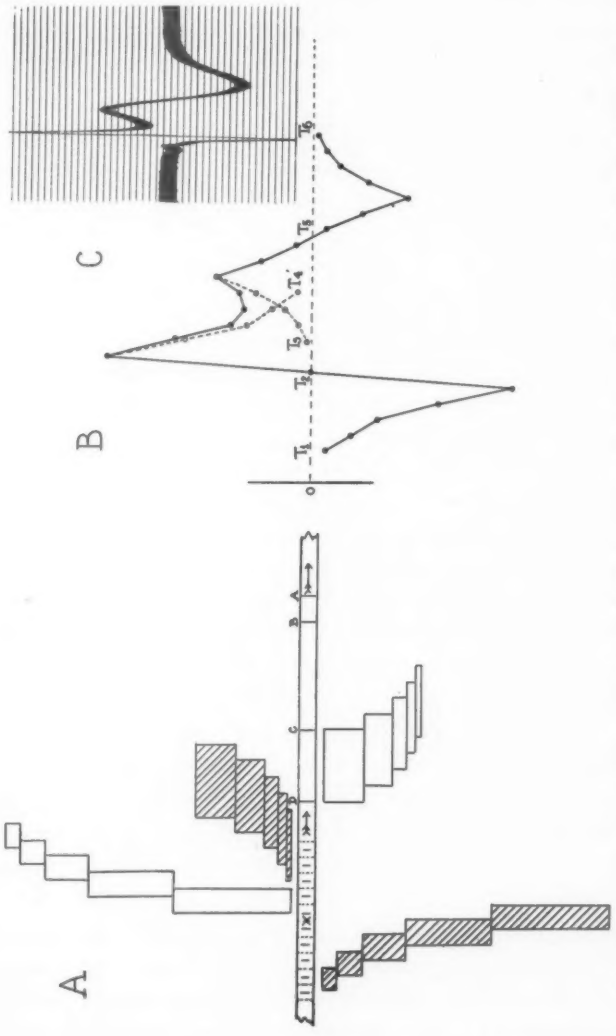

Fig. 9.—A is a plot of the electrical effects of each of ten muscle segments, five on either side of an electrode which is located one unit of distance toward the reader from *X*. *ABCD* is the excitation process; *AB* the stage of increasing activity, *BC* the stage of full activity, and *CD* the stage of decreasing activity.

B is a graph of the resultant electrical effects for each moment of time during the passage of the excitation process over the ten muscle segments represented in A—i.e., a synthetic electrogram. The dotted line starting at T_5 is a graph of the electrical effects of the regression of activity in the muscle elements to the left of the electrode plotted alone, and the dotted line ending at T_1 represents the electrical effects of accession of activity in the muscle elements to the right of the electrode plotted alone. (The full line in this region is a combination of these effects.)

C is an actual record taken from the central region of a frog's auricle after the preparation had been warmed.

closer, negative. By means of this formula the magnitude of the effect upon the electrode of any potential difference existing in any portion of the muscle can be calculated.

In the center of a long muscular fiber, divided into squares, is a cross (Fig. 9) which serves to indicate the position of the exploring electrode, the tip of which is supposed to be one unit of length above the plane of the paper. *ABCD* represents the familiar arrangement of the process of

activation and recovery. The effect upon the electrode of the electrical events which occur in the first square while its activity is increasing can be ascertained by applying the formula $E = \frac{\mu \text{ Cos } \theta}{R^2}$.* This effect on the electrode is represented in the figure by the first shaded rectangle below the muscle fiber (the first from the left). Its height corresponds to the electrical effect produced upon the electrode and its length to the duration of this effect. The duration will, of course, be equal to *AB*, since it is assumed that the velocity with which the process travels is one unit of distance in one unit of time. Once this element has become fully active it will no longer exhibit any potential difference. Thus, for the next seven units of time, no potential difference will exist here. But during the four and one-half units of time while activity is regressing (equal to *CD*) it again becomes the source of a potential difference, but this time of opposite polarity. This effect is represented by the first long narrow shaded rectangle above the muscle fiber. Since the regression process is three times as long as the period during which activity is increasing, the potential difference produced in a given segment in the first case is one-third that produced in the second. Consequently, this rectangle is one-third as high and three times as long as the one plotted for the period of increasing activity. Furthermore, since the positive pole is always toward the resting muscle, and the negative toward the active muscle in the case of increasing activity, the positive pole will be nearer the electrode and the effect upon it, therefore, positive, and in the case of decreasing activity, the negative pole will be nearer the electrode and the effect upon it negative. Since in electrocardiography the galvanometer is always so arranged that a negative effect produces an upward deflection, the negative effects are plotted above the base line (muscle fiber) and positive effects below.

Next, a similar plot is made of the electrical effects produced in the second square. The rectangles in this case are entirely similar to those for the first segment but both are of greater height, since the segment is closer to the electrode.

In the figure, rectangles have been constructed for each of ten segments, five to the left of the electrode (hatched), and five to the right (hollow). The effects of the segments to the right of the electrode must, obviously be of opposite polarity to those to the left, so that in this case the effects of increasing activity will be plotted above the line, and those of decreasing activity below. All the electrical effects produced are represented in their proper time relations. The first, that of increasing activity, starts when the excitation process reaches the muscle ele-

*In making the actual calculations for this graph and the ones to follow, the width of one square was used as the unit of length and μ given an arbitrary but appropriate value so that the resulting graph would be of a proper size. Negative effects are plotted above the line and positive effects below, to correspond to the conventional method of recording electrograms.

ment and endures so long as this transitional (increasing) state lasts. The second, that of decreasing activity, is plotted not over the muscle element in which it originates, but at the position corresponding to the *time* at which it occurs. Consequently, it is only necessary to take the sum of all the effects present at a given instant to obtain the height of the electrogram at this instant. Thus, any line drawn perpendicularly to the base line (muscle fiber) will cut one or more rectangles. If the segments of the intercepted rectangles are measured and added algebraically, the ordinate of the electrogram for that instant is obtained. Figure 9B is the theoretical electrogram so plotted. It will be seen that the *O* value of the ordinate at T_2 is the result of the sum of two equal but oppositely directed potential differences and not the nonexistence of a potential difference at this time. In the region to the right of T_3, effects of the regression of activity in segments to the left of the electrode are combined with effects of increasing activity in elements to its right, with the result that the curve does not return to the base line in this region. The dotted lines in the figure represent the effects of the accession and regression of activity in this region of overlapping, plotted independently. It is obvious from the figure that the electrogram is the sum of two diphasic curves, the first the result of the onset of activity, and the second the result of its regression, separated by an interval equal to the period during which each segment of muscle is fully active. It is to the second of these curves that particular attention will be directed, for adequate analyses of the former have already been made.

The recorded curve (Fig. 9C) was obtained from the frog's auricle by the method already described. Its similarity to the theoretical one is obvious. All the essential features of the recorded curve are present in the theoretical one. This particular curve was obtained from the central portion of the auricle after the preparation had been heated by flushing it with warm saline solution. It was chosen for the first analysis because it exemplifies the process in a more general way than do the curves taken under more nearly normal conditions which will be discussed presently. Craib, and Wilson, Macleod, and Barker believed furthermore, from their studies of the primary deflection, that the secondary or T deflection should be of this shape. But if such curves had been obtainable under ordinary circumstances, correct analyses of the secondary deflection undoubtedly would have been made long ago.

In the earlier part of this study the first rapid deflection (QRS) of the electrogram or electrocardiogram has been referred to as the primary, and the slower and later (T), as the secondary deflection. These terms are not satisfactory and were merely used as a convenient means of referring to the parts of the curve. But now that a probable causal relationship has been shown to exist between the first rapid diphasic curve (Fig. 9, $T_1T_2T_4$) and the accession of activity and the second

slower diphasic curve (Fig. 9, $T_3T_5T_6$) and the regression of activity, they will hereafter be designated as the accession deflection and the regression deflection.

It has been assumed that a muscle fiber is long enough to include all stages of activity at one time. But the conditions so far discussed do not represent the normal state of affairs. Obviously, since each small segment of muscle goes through every phase of activity, it is not at all necessary that fibers be long enough to contain at the same time, segments in each and every state from rest to full activity, and back again. It is permissible, therefore, to consider what may happen in a piece of muscle much shorter than the process of activity. In Fig. 10A is represented a short muscle fiber ten units long, the electrode located at the center but removed one segment's length from the plane of the page toward the reader. To the right, the excitation process is schematically represented. In the region *AB,* activity is increasing, in *CB,* it is fully developed, and in *CD,* it is decreasing. *CD,* the regression process, is more than twice as long as the muscle fiber. It is, of course, understood that length of process means merely the *time* during which activity is decreasing in a single muscle element, times the *velocity* with which the process travels.

If the electrical effects of each element in this short muscle are plotted as in the case of the long muscle fiber previously discussed, a graph similar to that in Fig. 9 is obtained (Fig. 10A). Figure 10B is the theoretical electrogram derived from the graph. The recorded curve (Fig. 10C) with which it is to be compared was obtained from the central region of the frog's auricle at room temperature, that is to say, under ordinary experimental conditions.

It will be noted that the electrogram, as before, is the sum of two diphasic curves, one produced by the electrical effects of increasing activity, and the other by the electrical effects of decreasing activity. Where the effects of decreasing activity (hollow rectangles) overlap those of increasing activity (shaded rectangles), the dotted line represents the effects of decreasing activity plotted alone. In this case it has been assumed that the muscle remains fully active for a short time only, so that the regression process (the effect of decreasing activity) begins very shortly after the accession process. The first phase of the regression process is, in these circumstances, entirely concealed in the larger accession process. This combination of effects necessarily distorts the accession deflection somewhat, rendering it asymmetrical. Since the portion of the regression process which is combined with the accession is an upward deflection, it slightly reduces the depth of the first downward phase of the accession deflection and augments the height of its upward phase. It is noteworthy also that while there is a long isoelectric region separating the first upward and second downward deflections of the regression process, this is the result of a balance between equal

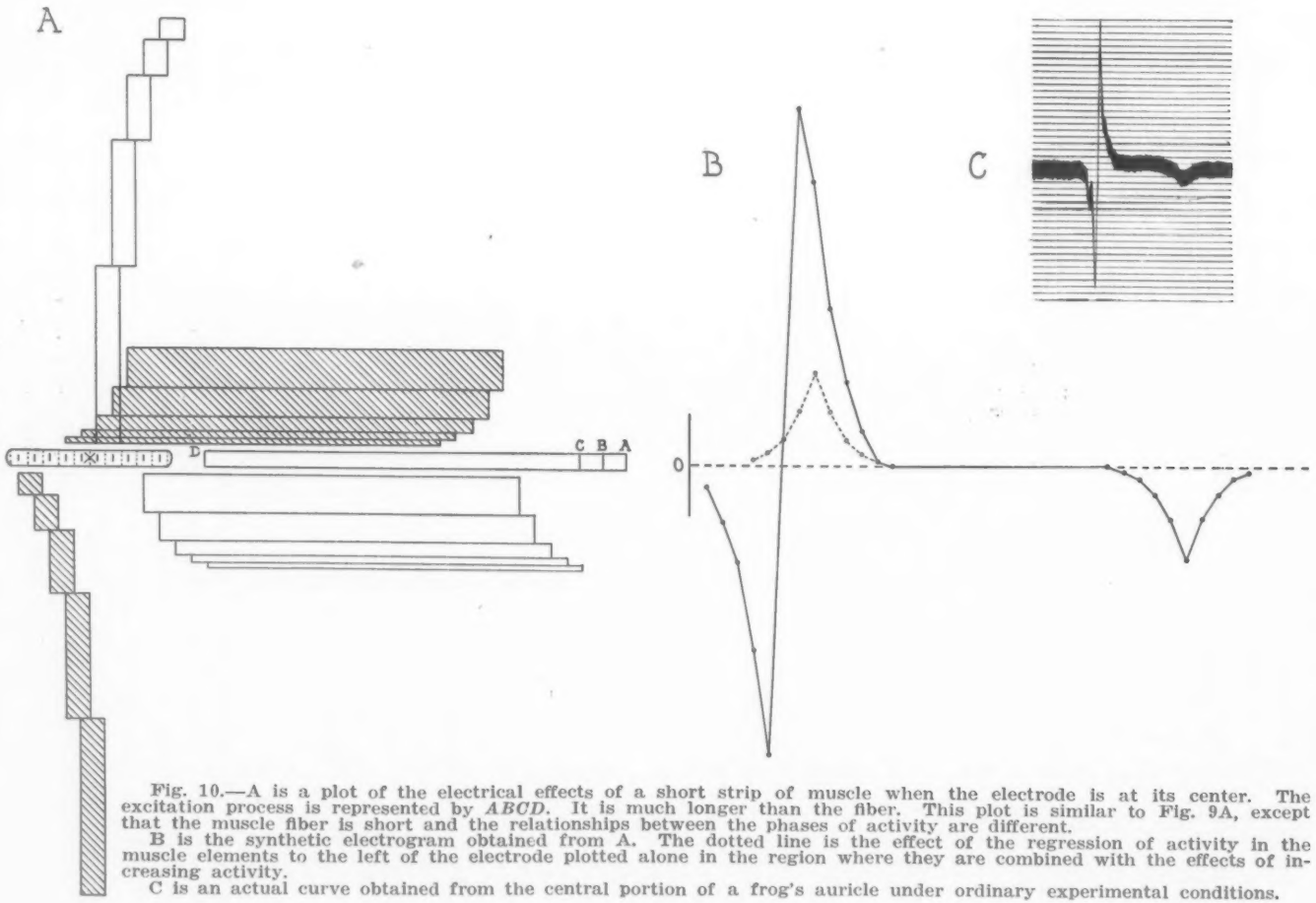

Fig. 10.—A is a plot of the electrical effects of a short strip of muscle when the electrode is at its center. The excitation process is represented by *ABCD*. It is much longer than the fiber. This plot is similar to Fig. 9A, except that the muscle fiber is short and the relationships between the phases of activity are different.

B is the synthetic electrogram obtained from A. The dotted line is the effect of the regression of activity in the muscle elements to the left of the electrode plotted alone in the region where they are combined with the effects of increasing activity.

C is an actual curve obtained from the central portion of a frog's auricle under ordinary experimental conditions.

and opposite effects in muscle units to either side of the electrode, and does not indicate that no electrical effects are present during this period. This point will be made clearer in the next two experiments.

If, instead of placing the electrode over the center of the muscle strip, it is placed nearer to one end (the end at which the impulse arrives latest) as in Fig. 11A, a distinct change in the type of curve obtained takes place. The graph of the electrical effects produced and the theoretical electrogram are constructed just as in the previous cases. The actual curve with which the theoretical electrogram is to be compared was obtained from the anterior surface of the frog's auricle near the auriculoventricular junction. The similarity between the theoretical and actual curves is again marked. The curve does not return to the base line after the end of the second phase of the accession process, but remains above the isoelectric line for a time and finally dips slightly below it. In this case, the sums of the electrical effects of the regression process in the muscle elements on either side of the electrode are unequal so that the curve does not coincide with the isoelectric line between its upward and downward peaks.

The reverse effect is obtained by placing the electrode near the other end of the muscle strip, that is to say, near the end at which the impulse arrives first (Fig. 12A). The recorded curve which is to be compared with the theoretical electrogram was taken with the exploring electrode near the sino-auricular junction. This record is less satisfactory than the curves illustrating the other cases because its last part is distorted by the occurrence of a ventricular beat, and because in order to expose the sino-auricular junction, the heart was pulled out of its normal position. But the expected features of the curve can be identified and are quite similar to the theoretical electrogram. In this case the portion of the regression process between the two peaks is below the isoelectric line because the equilibrium between the forces on the two sides of the electrode, acting during this interval, has been unbalanced in the direction opposite to that in the previous case.

DISCUSSION

It is apparent from these analyses that the regression deflection is, as Craib and Wilson, Macleod, and Barker believed, a curve of opposite phase to that of the accession deflection. Its first phase may be concealed within the accession deflection and between its upward and downward peaks there may be a portion parallel to the base line. Craib's qualitative reasoning was too indefinite and Wilson, Macleod, and Barker's mathematical analysis too cumbersome to bring out these facts clearly. Discussion of the quantitative relationships between accession and regression processes will be left for a future time but it is obvious that such relationships exist and that an analysis of the T deflection of

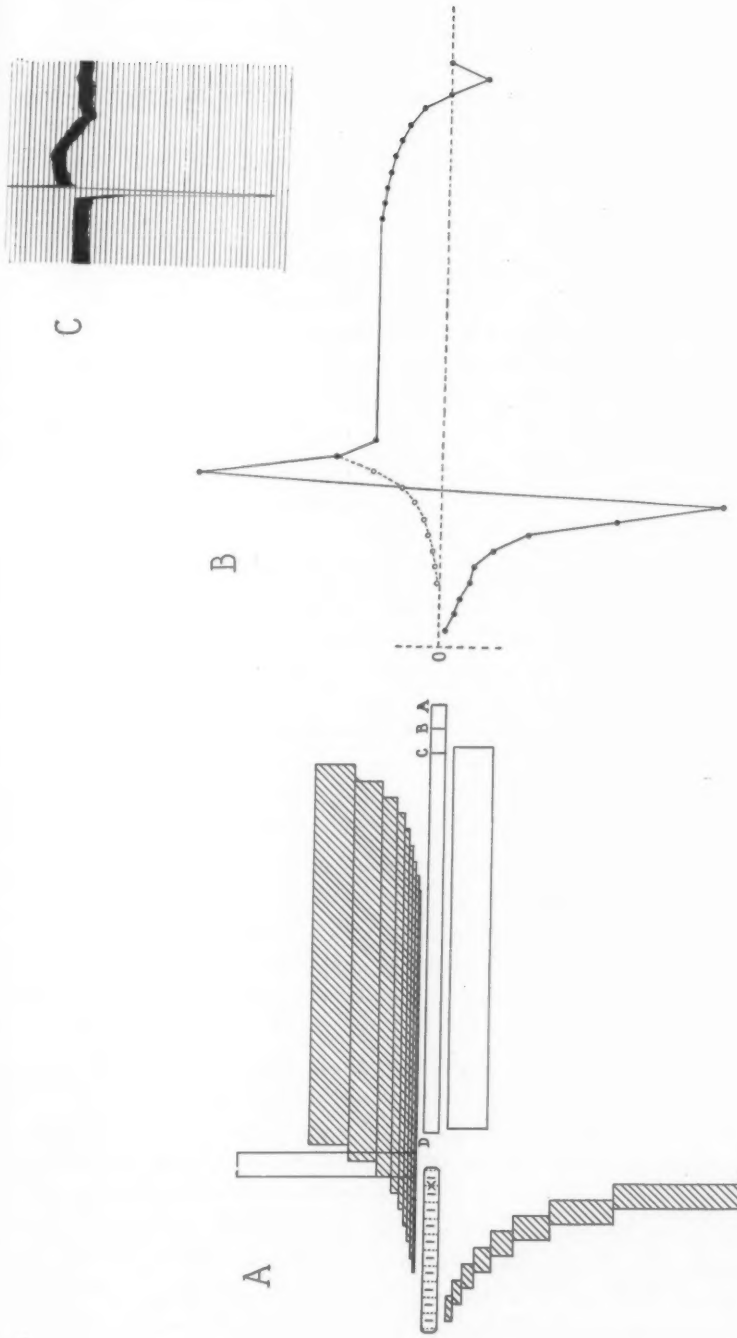

Fig. 11.—A is a plot of the electrical effects in a short strip of muscle when the electrode is near the end which the excitation process reaches last. *ABCD* is the excitation process. It is the same as in 10A.
B is the synthetic electrogram derived from A. The dotted line represents the effect of the regression of activity plotted alone.
C is an actual electrogram from a point on a frog's auricle near the auriculo-ventricular junction.

the electrocardiogram by means of the areas included by the complexes, such as Wilson, Macleod, and Barker[5] made, is appropriate.

Since there is evidence to indicate that the form of the electrogram is essentially the same for all forms of cardiac muscle, and since the time relationship between accession and regression processes is similar in electrograms (direct leads) and electrocardiograms (indirect leads), it is probable that part of the regression deflection of the electrocardiogram is really concealed in the accession deflection (QRS) and what has been called the S-T interval, is actually part of the regression deflection. That the S-T segment is an approximately straight line and either coincides with the isoelectric line or is parallel to it depends on the fact that the length of the regression process is longer than the course over which it travels. Coincidence of this portion of the curve (S-T) with the isoelectric line is, of course, fortuitous. If a large number of electrocardiograms is inspected, it will be found, in fact, that the coincidence is seldom exact. According to this view, what has usually been called the T-wave is only the last phase of the regression deflection.

In most discussions of this kind some mention is made of the membrane theory of Bernstein. The theoretical concepts in the early part of this paper are quite different in purpose from those of Bernstein. They do not, as do his, attempt to explain the entire mechanism of stimulation and conduction, but aim only to elucidate one phenomenon, the action current. Whereas Bernstein created an ingenious but imaginary construction which might account for the phenomena observed, the argument here presented consists of logical deductions from facts experimentally ascertained, according to accepted physical methods. Since most of these ideas are quite different therefore from any held by Bernstein when he described his theory, it seems inappropriate to attempt to correlate them with it.*

The assumption has been made that active and resting muscle differ in their constitution and that the contact potential between them gives rise to the action current. The first statement will hardly be denied and the second, since it is an undisputed fact that a potential difference exists between active and resting muscle, becomes self evident if the term contact potential is used in its broadest sense, and no attempt is made to define the possible mechanism by which it is produced. Consequently the argument which has been developed is independent of whatever may be discovered about the significance of minute anatomical structures and the chemistry of activation and recovery. It can shed no direct light on these subjects but may be able to furnish criteria useful in their investigation for it follows from the causal relationship shown to exist between the stages of increasing and decreasing activity and the acces-

*It is true that the potential difference between active and resting muscle can be accounted for by the membrane theory when properly interpreted[3] but the method used in the forepart of this paper is more direct and less confusing.

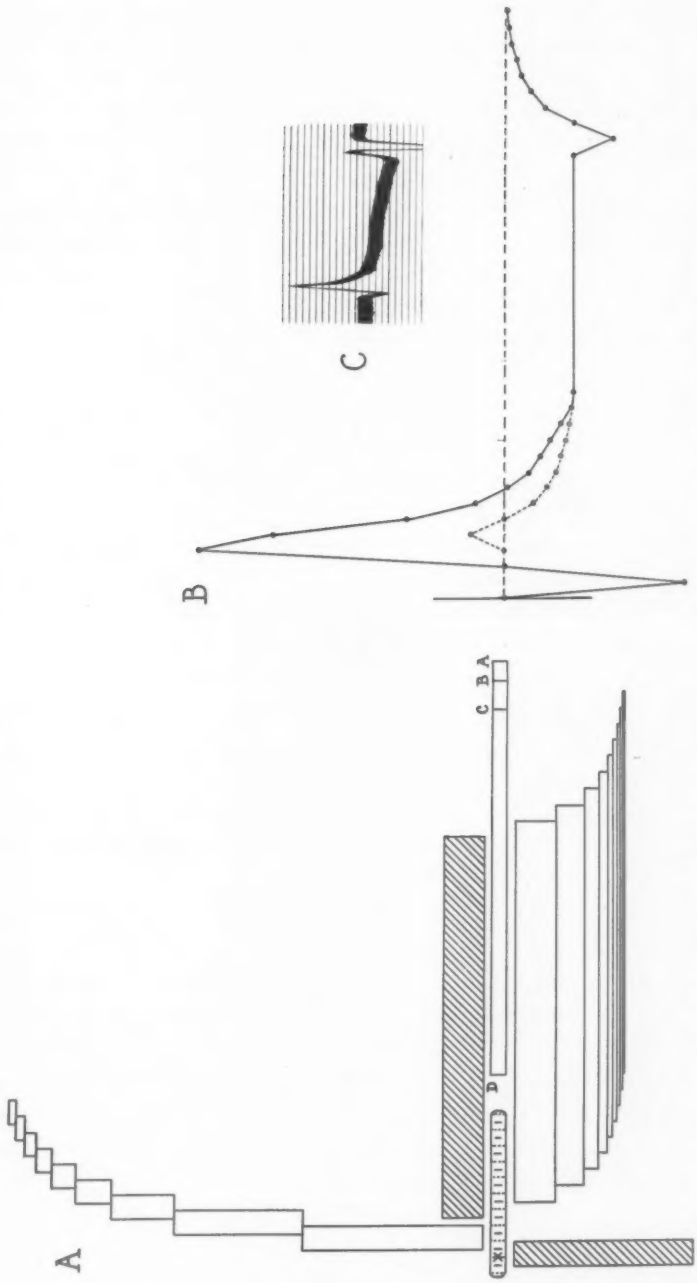

Fig. 12.—A is a plot of the electrical effect in a short strip of muscle when the electrode is near the end which the impulse reaches first. *ABCD* is the excitation process. It is the same as in 10A.

B is the synthetic electrogram derived from A. The dotted line represents the effect of the regression of activity plotted alone.

C is an actual electrogram from a point on a frog's auricle near the sino-auricular junction.

sion and regression deflections of the electrogram that it is possible to follow the course of the reactions, as yet unknown, which constitute the processes of activation and recovery.

SUMMARY

1. A method for recording electrograms from the uninjured frog's auricle has been described which approximate those obtainable from a simple strip of muscle.

2. Starting with the observation that a potential difference exists between active and resting muscle, an analysis of the processes of activation and recovery has been made. Based upon this analysis, a graphical method for the construction of a complete theoretical electrogram has been devised. Any assumptions regarding the properties of the excitation process may be made and the appropriate theoretical electrogram plotted. When a theoretical and an actual electrogram accurately correspond, the properties of the excitation process in the muscle which produced the actual curve are presumed to be similar to those assumed in constructing the theoretical one.

3. The regression, like the accession deflection, is expressed in a diphasic curve, the central portion of which may be parallel to the isoelectric line.

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EFFECTS OF INDUCED OXYGEN WANT IN PATIENTS WITH CARDIAC PAIN*

ROBERT L. LEVY, M.D., ALVAN L. BARACH, M.D.,
AND HOWARD G. BRUENN, M.D.
NEW YORK, N. Y.

THE precise mechanism by which painful impulses are initiated in the heart is, as yet, imperfectly understood. There is much evidence to indicate that cardiac pain is due to chemical irritants, presumably acid in character, which are formed during muscular contraction, and that ischemia plays an important causative rôle.[1] Reduction or cessation of blood supply may bring about an increased accumulation of such acid metabolites or may result in failure of the circulation to wash away these substances from the cardiac tissues. Whether the lack of oxygen is itself the stimulus, or whether a pain-producing substance is formed as the result of anoxemia, is not clear.

The present study was undertaken in order to observe the effects of induced, systemic oxygen want in relation to various other factors. Our procedure differed from those previously employed in that (1) a special apparatus was devised by means of which the patient could breathe a constant percentage mixture of oxygen at a rate comparable to that of the normal pulmonary ventilation; (2) the level of anoxemia reached was ascertained by determining the oxygen saturation of the arterial blood; (3) the arm-to-tongue circulation time was measured before and during the test.

TECHNIQUE

Apparatus (Fig. 1).—A tank containing 12 per cent oxygen and 88 per cent nitrogen was used to maintain an unvarying concentration of oxygen in the inspired air. The oxygen mixture was admitted at a rate that was comparable to the normal pulmonary ventilation. The bag was kept full but not distended. By the use of two flutter valves the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while breathing room air and thus accurately to record the time that he was exposed to inhalation of a low oxygen mixture. A tank containing 100 per cent oxygen was also in the circuit, so that if necessary, by turning a needle valve, anoxemia could be quickly relieved. At the end of each period of observation, the patient was permitted to breathe pure oxygen for several minutes.

Procedure.—Observations were made at least two hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Clinic of the Presbyterian Hospital.

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at about 68° F. The patient was allowed to rest in bed for a period varying from twenty minutes to one hour. The procedure was explained and the patient was told that as soon as he experienced pain in the chest or arms, he should raise his hand. A sample of arterial blood taken from the brachial artery was then obtained under oil. The needle for the venous pressure apparatus was next inserted into one of the veins of the arm and a free flow of the column of fluid was assured before proceeding. Through this needle, which was attached to a three-way stopcock, 5 c.c. of a 20 per cent solution of sodium dehydrocholate was injected and the circulation time, using a bitter taste as the end point, was measured in seconds with a stop watch. The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted. The patient was allowed to breathe ordinary air through the valve of the apparatus for a few minutes. Control readings of pulse, respira-

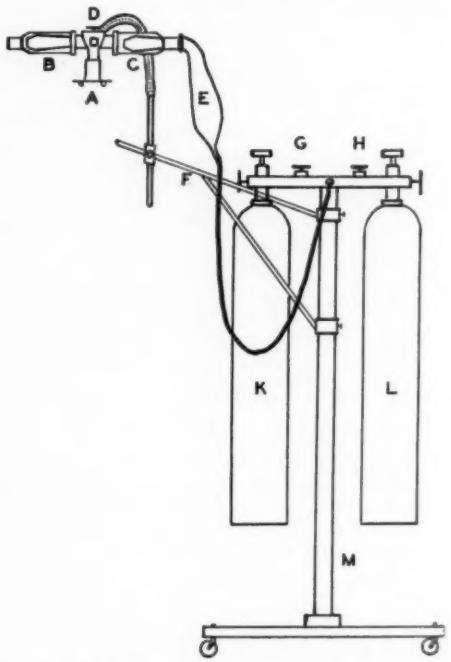

Fig. 1.—Apparatus. *A*—Mouthpiece. *B*—Expiratory flutter valve. *C*—Inspiratory flutter valve. *D*—Mouthpiece control valve. *E*—Bag. *F*—Support stand. *G*—Nitrogen-oxygen mixture needle valve. *H*—Oxygen needle valve. *K*—Tank containing mixture of 88 per cent nitrogen and 12 per cent oxygen. *L*—Tank containing pure oxygen. *M*—Tank carrier.

tion, blood pressure, and venous pressure were made until an equilibrium had been reached. The test was then started by turning valve D, as shown in Fig. 1. If pain was experienced the low oxygen mixture was immediately shut off and 100 per cent oxygen was administered. The period of observation was usually no longer than twenty minutes and was never continued longer than twenty-eight minutes. Records of the pulse, respiration, blood pressure, and venous pressure were taken every few minutes. The arterial oxygen saturation and circulation time were determined again only at the conclusion of the experiment.

The above procedure was followed, but without the blood analyses and venous pressure determinations, in those cases in which electrocardiograms were taken. In such experiments, a control record was made and additional curves were taken throughout the period of observation at intervals of several minutes.

MATERIAL

Observations were made on 37 patients with cardiac disease.* Seventy tests were performed; electrocardiograms were taken in ten of these. The clinical diagnoses were: coronary sclerosis with cardiac pain, 30 cases; coronary sclerosis with rheumatic aortic insufficiency, 1; hypertensive heart disease with cardiac pain, 2; aortic stenosis with cardiac pain, 2; syphilitic aortitis and aortic insufficiency, with cardiac pain, 1; rheumatic heart disease with mitral stenosis and insufficiency, 1.

Eleven additional patients without cardiac disease served as controls. The same procedure was applied to them.

RESULTS

Cardiac Pain.—Three of the 37 patients with heart disease did not complain of spontaneous pain; in them, no pain was induced by anoxemia. Of the remaining 34 who gave a history of anginal attacks, only a single observation was made on 23. Of these, 9 had pain during the test; 14 had no discomfort.

In 14 cases, more than one test was done. In 4 patients, no pain occurred. In 7, the result was variable, the patient on some occasions complaining of pain, at other times failing to do so. This variability in response to anoxemia was striking and, it seems to us, important, particularly when compared to the invariable, prompt and sharp response in 2 patients with aortic stenosis. The significance of these results will be considered in the discussion.

In none of the 11 patients without cardiac disease did pain occur.

Heart Rate.—There were 58 observations in 37 cardiac patients. In 34, the rate was accelerated; in 6 there was no change; in 5 the rate was slower at the end of the experiment than at the beginning; in 13 there were slight fluctuations.† There was no correlation between alterations in rate and the occurrence of pain.

Respiratory Rate.—There were 57 observations in 37 cardiac patients. The rate increased in 35; in 3 it was unchanged; in 5 it became slower; in 14 there were slight fluctuations.‡ As was the case with the pulse rate, there was no demonstrable relationship between the respiratory rate and the occurrence of pain.

Blood Pressure.—There were 58 observations in 37 cardiac patients. The systolic level rose in 30; in 4 it was unchanged; in 9, it fell; in 15 there were slight fluctuations.§ The diastolic level rose in 24; in 10 it was unchanged; it fell in 12; in 12 there were slight fluctua-

*We are indebted to Dr. Harold J. Stewart for referring a number of patients from the Cardiac Clinic of the New York Hospital; and to Dr. Arthur C. DeGraff for sending one patient from the Cardiac Clinic of Bellevue Hospital.

†A change of 10 beats or more per minute was considered significant.

‡A change in rate of 4 or more per minute was considered significant.

§A change of 10 mm. Hg or more was considered significant.

tions. Both systolic and diastolic pressures rose more often in the cases that developed pain, and fell more frequently in those that did not. But the association was not invariable. The actual changes observed were relatively small; in only 13 instances did the systolic pressure fluctuate more than 20 mm. Hg; and in only 4 did the diastolic vary to this extent.

*Venous Pressure.**—There was no definite trend in the 18 cardiac patients in whom this was determined. Of the group, 6 experienced pain; and included in this number were the 2 patients with aortic stenosis. In 4 of these 6 patients, a rise in venous pressure occurred, ranging from 12 to 35 mm. of water. Of the 12 cases which did not have pain, 4 showed a higher reading at the end of the experiment

TABLE I

PROTOCOL OF A TYPICAL EXPERIMENT

M. H., male, aged 69. *Diagnosis:* Hypertension; cardiac hypertrophy; sclerosis of coronary arteries; cardiac pain. (Electrocardiogram showed sinus rhythm; left bundle-branch block; prolonged A-V conduction; T_1 ±; T_2 and T_3 +; T_4 −).

TIME	PULSE RATE	RESPIRATORY RATE	BLOOD PRESSURE	VENOUS PRESSURE (MM. H_2O)	ARTERIAL O_2 SATURATION (PER CENT)	CIRCULATION TIME (SECONDS)	REMARKS
10:00							In bed
10:50							Venous pressure needle inserted
11:00					93.6		Sample of arterial blood
11:05	80	24	200/122	81			
11:06				80			
11:07						27	
11:09	80	26	200/118	65			Control
11:10	80	24	200/120	64			Control
11:10½	76			64			Control
11:11							12 per cent O_2 started
11:11½	80	23	190/124	65			
11:12½	84	24	198/126	72			
11:13½				84			
11:14	84	24	218/130	88			
11:15	84	23	200/120	84			
11:16	76	24	194/110	71			
11:18	74	30	168/90	60			
11:19	74	29		50			
11:20			168/98				
11:20½	78	29		53			Pain*
11:21					70.2	16	Sample of arterial blood
11:22							100 per cent O_2 given

*Pain described as "the same as when I walk." It was precordial, with radiation to the right arm.

*Venous pressure was measured by the direct method of Moritz, F., and von Tabora, D.: Über eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsch. Arch. f. klin. Med. 98: 475, 1910.

than in the control readings. The average duration of the experiment was longer in the group without pain—an average of nineteen minutes as compared with eleven for the group with pain.

*Circulation Time.**—This was measured in 18 patients with cardiac disease and in 11 persons with normal hearts (Table II). In some of the cardiac patients the control reading was a little longer than the upper limit of twenty-one seconds observed by others in similar cases without myocardial insufficiency.[2] This may have been due to the presence of a mild degree of latent left ventricular failure. Except in the two patients with aortic stenosis, the circulation time invariably decreased, that is, the rate of flow became faster. In 5 patients, pain appeared after an average interval of nine minutes, and the average shortening in circulation time was six seconds. In the 10 patients without pain, the average duration of the experiment was twenty minutes and the average shortening was five seconds.

In the two patients with aortic stenosis, the circulation time did not change. This was in sharp contrast to the acceleration observed in the other cardiac cases.

As a general rule, the increased velocity of the circulation was proportional to the increase in heart rate. In about one-third of the cases, however, this relationship did not obtain. In the patients with aortic stenosis, the heart rate increased 26 beats in one instance and fell 12 beats in the other.

In the 11 persons with normal hearts, the changes in circulation time after eighteen to twenty minutes of anoxemia were relatively small, the maximum being a decrease of 4.8 seconds (Table II). Evidently other mechanisms can compensate in large measure for oxygen want, provided there is no cardiac impairment.

Arterial Oxygen Saturation.†—This was determined in 17 persons with cardiac disease and in one normal person (Table II). The control levels ranged from 93.3 to 97 per cent, with four exceptions. In two instances, the control specimens were taken fifteen to eighteen minutes after the conclusion of the experiment, instead of before beginning it (Cases 3 and 23, Table II). The values were 90 and 91 per cent respectively; evidently a proper gaseous equilibrium had not been reestablished. In two other cases the control values were a little low —89.6 and 92.5 per cent respectively. In one of these, emphysema was present; in the other there was profound anemia (Cases 4 and 5, Table II).

*Circulation time was measured according to the method of Winternitz, M., Deutsch, J., and Brill, Z.: Eine klinische brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, Med. Klin. 27: 986, 1931; ibid. 28: 831, 1932.

†Arterial oxygen saturation was determined by the method of Van Slyke, D. D., and Neill, J. M.: Determination of Volumes of Gases in Blood by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. 64: 543, 1924.

TABLE II

EFFECTS OF INHALATION OF 12 PER CENT OXYGEN MIXTURE ON ARTERIAL OXYGEN SATURATION AND CIRCULATION TIME IN 23 PATIENTS WITH CARDIAC DISEASE AND IN 7 PERSONS WITH NORMAL HEARTS

CASE NO.	CLINICAL DIAGNOSIS	AGE	SEX	ARTERIAL OXYGEN SATURATION (PER CENT)		CIRCULATION TIME (SECONDS)		PAIN	DURATION OF EXPERIMENT (MINUTES)	REMARKS
				CONTROL	AT END OF EXPERIMENT	CONTROL	AT END OF EXPERIMENT			
1.	Coronary sclerosis	62	M	97.0	72.2	27.8	20.5	0	20	
2.	Coronary sclerosis	66	M	95.2	84.6	-	-	0	20	Had received paravertebral alcohol injections
3.	Coronary sclerosis	71	M	90.0*	63.5	21.0	15.0	0	20	*Specimen taken fifteen minutes after conclusion of experiment
4.	Coronary sclerosis	57	M	89.6	62.6	21.4	-	0	20	Had marked emphysema
5.	Coronary sclerosis	48	M	92.5	50.1	-	-	+	12	Had profound anemia
6.	Coronary sclerosis	61	M	96.6	67.8	37.0	34.0	0	18	Red blood count 2.5 million
7.	Coronary sclerosis	69	M	93.6	70.2	27.0	16.0	+	10	Went into shock
8.	Coronary sclerosis	62	M	95.5	76.2	-	-	0	20	
9.	Coronary sclerosis	51	M	-	-	26.2	26.0	0	6	Pressure on chest; experiment stopped
10.	Coronary sclerosis	51	F	96.0	68.5	11.8	11.2	+	12	
11.	Coronary sclerosis	70	M	95.7	67.6	21.4	17.6	0	20	
12.	Coronary sclerosis	56	M	-	-	28.2	20.0	+	5	
13.	Coronary sclerosis	58	M	96.5	79.0	14.8	13.4	0	20	

TABLE II—CONT'D

14.	Coronary sclerosis	55	M	93.3	68.6	15.6	12.4	0	24	
15.	Coronary sclerosis	48	F	–	–	15.0	16.2†	+	20	†Only 2.5 c.c. decholin given
16.	Coronary sclerosis	41	F	–	–	26.0	16.5	0	20	
17.	Coronary sclerosis; rheumatic heart disease; aortic insufficiency	62	M	95.4	73.3	27.0	20.0	0	20	
18.	Rheumatic heart disease; mitral stenosis and insufficiency	38	M	94.8	82.8	–	–	0	20	
19.	Aortic stenosis	44	F	–	–	17.2	18.2	+	14	
20.	Aortic stenosis	55	M	95.3	68.5	18.0	18.5	+	19	
21.	Syphilis of aorta; aortic insufficiency	35	F	94.6	76.2	18.0	15.0	0	28	
22.	Syphilis of aorta; aortic insufficiency	35	F	–	–	21.2	13.2	+	13	
23.	Hypertension; arteriosclerosis; auricular fibrillation	69	M	91.0‡	74.2	–	–	0	23	‡Specimen taken eighteen minutes after conclusion of experiment
24.	Normal heart	32	M	96.6	67.8	17.6	17.0	0	18	
25.	Normal heart	45	M	–	–	13.2	12.0	0	20	
26.	Normal heart	59	M	–	–	16.4	14.8	0	20	
27.	Normal heart	35	F	–	–	11.4	9.8	0	20	
28.	Normal heart	33	F	–	–	14.9	13.8	0	20	
29.	Normal heart	46	M	–	–	17.8	13.0	0	20	
30.	Normal heart	63	F	–	–	13.4	13.4	0	20	
31.	Normal heart	33	M	–	–	15.8	11.8	0	18	
32.	Normal heart	36	M	–	–	13.7	10.8	0	18	
33.	Normal heart	41	M	–	–	14.8	12.0	0	18	
34.	Normal heart	32	M	–	–	11.6	9.2	0	18	

In every case, there was marked lowering of the arterial oxygen saturation, the values at the end of the observation period ranging from 50.1 to 82.8 per cent. Excepting the four cases referred to in the preceding paragraph, the lowest level of saturation was 67.6 per cent. In the one patient with a normal heart in whom the arterial oxygen content was determined, the level fell from 96.6 per cent to 67.8 per cent. The degree of cyanosis was, in general, proportional to the degree of unsaturation. But there was no apparent relationship

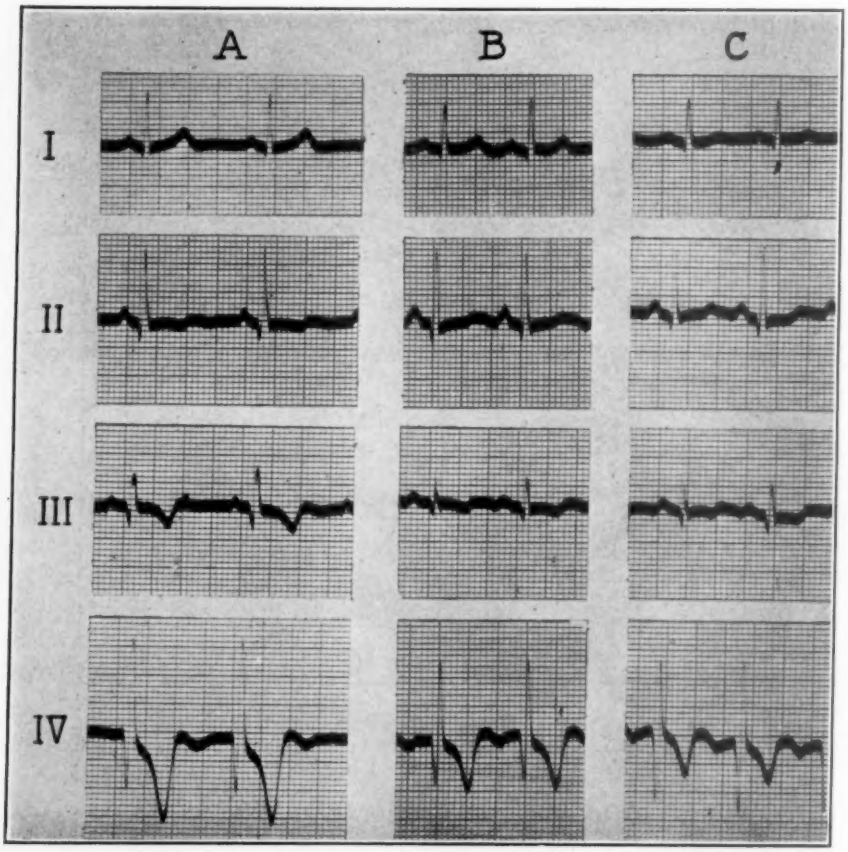

Fig. 2.—Patient with coronary sclerosis and cardiac pain. *A*—control. *B*—after inhaling 12 per cent oxygen for one minute. *C*—after six minutes. Note changes in the contour and amplitude of the T-waves in all leads. The changes in the R-T and S-T segments are slight and are most marked in Lead IV.

between the degree of anoxemia and the appearance or severity of cardiac pain. Nor did the level of oxygen saturation run parallel with increase in heart rate or decrease in circulation time.

Electrocardiograms.—These were taken in 10 patients with cardiac disease. Changes in form were observed in all; in each instance the T-waves altered their amplitude and, occasionally, their direction (Fig. 2). In seven cases, the R-T or S-T segments became depressed in the

three standard leads or elevated in Lead IV (Fig. 3). The heart rate was uniformly accelerated. The auriculoventricular conduction time remained remarkably constant.

In 8 patients without heart disease, changes in the form of the records were also observed in all, but they were of relatively minor degree (Fig. 4). In seven, the T-waves were slightly flattened; in two the R-T or S-T segments were a little depressed. The rate was always increased.

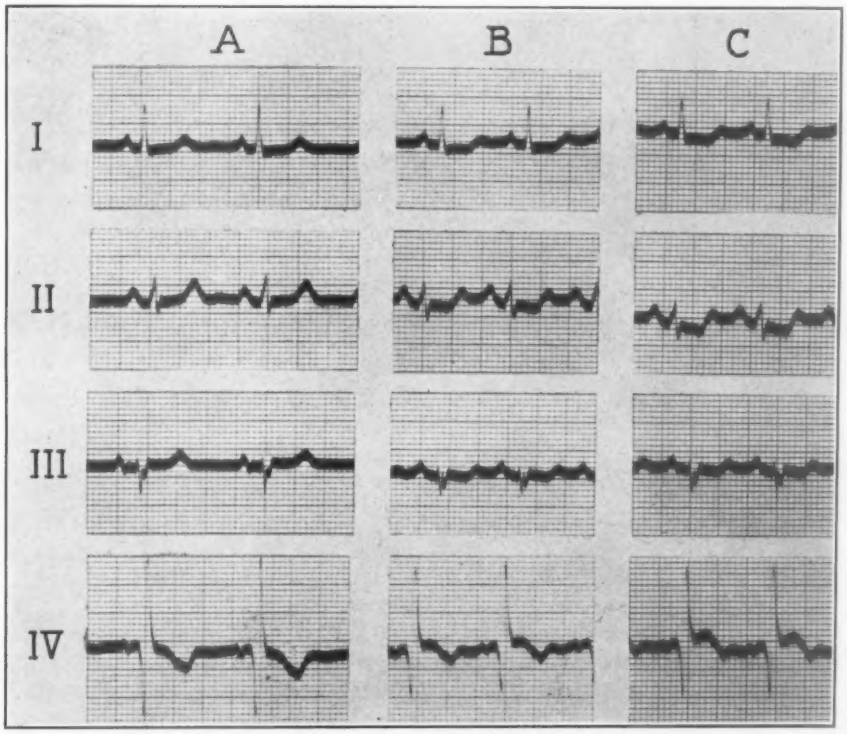

Fig. 3.—Patient with coronary sclerosis who had been given paravertebral injections of alcohol with almost complete relief of cardiac pain. *A*—control. *B*—after inhaling 12 per cent oxygen for thirteen minutes. *C*—after seventeen minutes. Note depression of R-T and S-T segments in the three standard leads, and marked elevation in Lead IV. There are also changes in the amplitude of the T-waves.

Untoward Effects.—In two patients, unpleasant reactions occurred. The first, a man, aged sixty-five years, with coronary sclerosis and cardiac pain, had suffered from an attack of coronary thrombosis seven years previously. The signs indicated that an aneurysm of the left ventricle had developed. Six minutes after beginning the inhalation of 12 per cent oxygen, an attack of typical pulmonary edema appeared. An injection of morphine was given and he was kept in bed in the hospital until the following morning. He was then able to return to his home and experienced no further ill effects.

The second patient was a man, aged sixty-one years, with coronary sclerosis and cardiac pain. He, too, had recovered from an attack of coronary thrombosis three years before. A healed infarct of the myocardium was present, without demonstrable aneurysmal dilatation of the ventricle. Ten minutes after beginning to breathe the low oxygen mixture, the blood pressure began to fall and within another five minutes had dropped from 130/80 to 98/54. The venous pressure fell, coincidently, from 46 to 6 mm. of water. He presented the picture

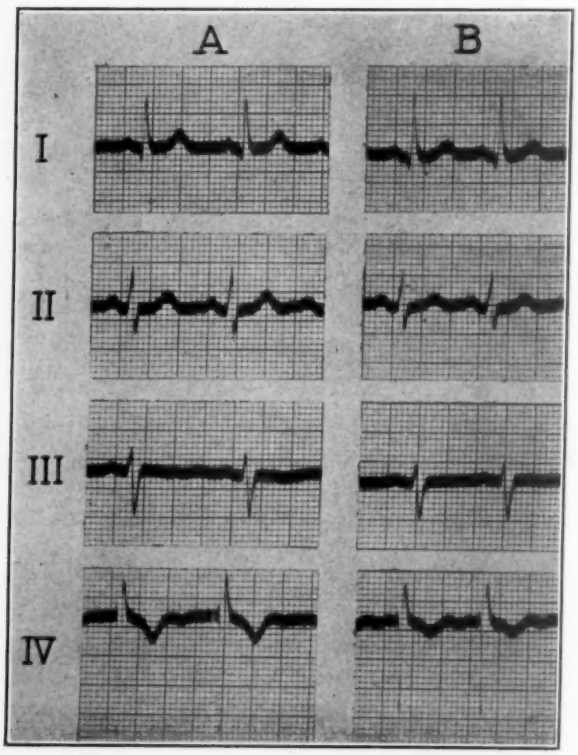

Fig. 4.—Patient with normal heart. *A*—control. *B*—after inhaling 12 per cent oxygen for twenty minutes. Note slight flattening of the T-waves in Leads I and II; and less deeply inverted T-wave in Lead IV. There is no effect on the R-T or S-T segments.

of shock. Pure oxygen was administered through the apparatus and ten minutes later the blood pressure had returned to its initial level, although he was still shaky and cold. No cardiac pain was felt by either of these men; presumably the nerve endings in the scarred areas of heart muscle had been destroyed or rendered insensitive to painful stimuli.

A number of patients complained of transient dizziness and dryness of the mouth; but there were no other disturbing incidents.

COMMENT

Other observers, using rebreathing methods, have commented on the inconstancy with which cardiac pain occurs on the induction of generalized anoxemia in patients with spontaneous attacks.[3] Rothschild and Kissin noted also the lack of relationship between the oxygen level of the inspired air and the onset of discomfort. They concluded that the response to induced oxygen want was of value in the diagnosis of an impaired coronary circulation. Katz, Hamburger, and Schutz, on the other hand, decided that because of the variability in the results and of the hazard to the patient, "the use of induced anoxemia as a test for the presence of angina pectoris is of questionable value."

Our results, though confirming the variability with which pain occurs, may be interpreted in a manner which will serve to reconcile this difference in point of view. It is understood, of course, that what is said applies only under the conditions of these experiments, namely, a relatively short period of anoxemia and levels of arterial saturation ranging from 67 to 83 per cent. In addition to having shown that pain is not invariably caused by induced oxygen want in different patients with spontaneous attacks, our observations have stressed the inconstancy of its occurrence in the same patient at different times.

The inconstancy in response was not related to changes in heart rate, arterial blood pressure, or venous pressure. There was no critical level of arterial oxygen unsaturation at which pain occurred. But in all cases of cardiac disease studied, with two exceptions, the circulation time decreased—that is, the rate of flow became faster and, presumably, the cardiac output increased.[4] At times the increased blood supply to the myocardium was sufficient to counteract the effects of the lowered concentration of oxygen. In the two patients with aortic stenosis, repeated tests (6 in one case, 3 in the other) resulted in the prompt and invariable causation of pain. It was in these two cases that oxygen want did not induce a change in the circulation time. That the coronary blood flow is reduced in aortic stenosis has been demonstrated by Green.[5] Because of mechanical obstruction to the outflow of blood from the left ventricle, acceleration of the rate of flow and coincident increase in cardiac output cannot become operative as compensating mechanisms. Coronary insufficiency, with ischemia of the myocardium, results. In the presence of oxygen want, pain is produced.

Anoxemia, then, must be regarded as an important factor in the causation of cardiac pain. Probably it is not the sole cause.[6] It is most effective when the coronary flow is reduced; its importance varies directly in proportion to the extent of such reduction. Anoxemia appears to be the determining factor in the process, in the sense that pain occurs only when the supply of oxygen is inadequate. Ischemia

and anoxemia complement each other in synergistic fashion as pain-inducing agents in the heart; neither is wholly effective alone. Thus, extreme anoxemia does not cause cardiac pain in the normal person in whom compensating mechanisms in the circulation are able to function; conversely, the pain following coronary occlusion is often partly or completely relieved by the administration of oxygen.[7]

A number of circumstances are undoubtedly concerned. Of great importance is the emotional status of the patient, as well as his usual ability to appreciate painful sensations.[8] Other variables are the degree of sensitivity of the afferent nerve endings in the heart, the state of the nervous pathways which conduct pain impulses from the heart to the central nervous system, the total metabolism of the patient and the oxygen-carrying capacity of the blood.

The changes in the form of the electrocardiogram which we have recorded have been previously noted.[9] They are not specific, for similar alterations can be induced by a number of other conditions. Their description has been included merely to indicate that they occurred under the conditions of these tests. It is well to emphasize that they occurred in patients with normal hearts as well as in those with cardiac disease, but that the degree of change was far greater when the coronary circulation was impaired.

The induction of pulmonary edema and of shock in patients with coronary insufficiency and a damaged myocardium is of practical importance in relation to the effects of oxygen want at the high altitudes encountered in aeroplane flights.* An oxygen concentration of 12 per cent in the inspired air is equivalent, approximately, to an altitude of 15,000 feet. Persons known to have cardiac disease due to an affection of the coronary arteries should not be permitted to ascend to high altitudes.

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*Since our paper was written, a remarkable case bearing on this point has been reported by Capt. O. O. Benson, of the Medical Corps, U. S. Army (Coronary Artery Disease: Report of a Fatal Cardiac Attack in a Pilot While Flying, J. Aviation Med. 8: 81, 1937). An officer of the Air Corps, aged thirty-four years, had served throughout the war in France. He was a vigorous, healthy man, somewhat overweight. There was nothing in the history to indicate the presence of cardiovascular disease. The blood pressure had always been normal. In November, 1935, while piloting an airplane over the Tehachapi Pass in California, he suddenly experienced a severe pain in the chest. He was the only pilot in the plane, which contained several passengers. Despite agonizing pain, he flew for twenty minutes longer and landed without mishap. He was put to bed at once by a medical officer. Pain continued, cyanosis increased, and he died about an hour later.

At necropsy the heart weighed 441 gm. In the right coronary artery there were several superficial patches of atheroma, but no gross involvement of the smaller branches was seen. The descending branch of the left coronary artery, about 2.5 cm. beyond its point of origin, showed extensive atheroma, involving almost the entire intima to within a short distance of the cardiac apex. The lumen was not much compromised. The circumflex branch was affected in similar fashion. The aorta was practically free from pathologic change. The leaflets of the aortic valve were very slightly thickened. There were several small yellowish patches of atheroma about the base of the aortic leaflet of the mitral valve. No thrombi or emboli were found. There was no infarction of the myocardium. The other organs were normal.

Microscopically, a few of the fibers of the heart muscle were hypertrophied. The medium-sized arteries were sclerosed. There was scarring in the septum, and about one-quarter of the fibers of the main auriculoventricular bundle were destroyed by fibrosis.

Benson remarks that "there is sufficient pathologic change in the heart to justify the conclusion it was the cause of death, precipitated by an attack of angina. Should the pilot's death have occurred in the air with the resultant crash of the plane and death to the other occupants, the conjectures as to the cause of the accident would have been myriad, no doubt. Structural failure of the plane would probably have been the generally accepted explanation."

If such a flight is imperative, provision must be made for supplying the necessary concentration of oxygen.

It is possible that a procedure such as the one described in this paper will prove useful as a test for the functional efficiency of the coronary circulation. It may be expected to detect only those instances in which the coronary reserve is markedly diminished and in which there is failure of compensation under stress. These are the patients in whom acute coronary insufficiency and, on occasion, sudden death are likely to occur.[10] But further studies are necessary to define more precisely the applicability, limitations, and dangers of such a test; at present, it is not recommended for general use.

SUMMARY

1. An apparatus has been described for inducing systemic oxygen want in patients, without rebreathing.

2. Observations were made on 37 patients with cardiac disease and on 11 with normal hearts. A level of oxygen saturation was reached ranging from 67 to 83 per cent, as determined in samples of arterial blood.

3. There was no constant relationship between the occurrence of cardiac pain and changes in heart rate, respiratory rate, blood pressure, venous pressure, circulation time and the degree of arterial unsaturation.

4. Pain occurred inconstantly in repeated tests, except in two patients with aortic stenosis and in one with advanced coronary lesions. In the two patients with aortic stenosis there was no compensatory shortening of the circulation time during the anoxemic period.

5. Untoward effects were observed in two patients with healed infarcts of the heart. Both recovered promptly. The bearing of these experiences on the danger of aeroplane flights for persons with disease of the coronary arteries was discussed.

6. Oxygen want is an important, and apparently the determining factor in the causation of cardiac pain. It is most effective when the coronary blood flow is reduced. Ischemia and anoxemia complement each other as pain-inducing agents in the heart. Other variable circumstances are also concerned.

7. The induction of systemic oxygen want may prove to be useful as a test for coronary insufficiency; it is not recommended for general use at this time.

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THE IMMEDIATE EFFECT OF MERCURIAL DIURETICS ON THE VITAL CAPACITY OF THE LUNGS*

JOHN B. ALSEVER, M.D., SYRACUSE, N. Y., AND SAMUEL A. LEVINE, M. D., BOSTON, MASS.

IT IS the purpose of this paper to present some definite evidence concerning the value of diuretics in improving the respiratory function in patients with heart failure. There have been but few published communications concerning the direct and immediate effects of diuretics on dyspnea, although many authors comment on their value.[1, 2, 3] It is generally known that the more powerful diuretics like mercupurin and salyrgan are of great help in the presence of congestive failure with peripheral edema, but such improvement in breathing as results from their use might be ascribed to the prolonged rest in bed, digitalis, and other therapeutic measures. It is obvious that the disappearance of edema results directly from the diuretic drug. To appraise the effect of a diuretic on the factor of dyspnea alone it would be preferable to study its effect in cases with no peripheral pitting edema. Harrison[4] and Friedman, Resnik, Calhoun, and Harrison[5] have reported a few observations that bear directly on this problem.

A small group of cardiac patients was selected, suffering from breathlessness, in whom there was no evidence of peripheral edema or in whom the edema was only moderate in degree. In most instances the diuretic used was 1 or 2 c.c. of mercupurin given intravenously. In a few cases a similar amount of salyrgan or a mercupurin suppository was given. All the patients were under bed care in the hospital, had been digitalized, and generally were taking ammonium chloride. The specific effect of the diuresis on the respiratory mechanism was judged by measuring the vital capacity of the lungs just before the diuretic was injected and repeating this observation twenty-four hours later. Subjective changes in the degree of dyspnea were also estimated, and changes in the physical findings in the lungs, such as the presence or absence of râles, were noted. The most reliable measure of improvement in breathing has been found to be the vital capacity of the lungs. This objective figure eliminates the error that might otherwise result in estimating a subjective sensation such as respiratory distress.

Table I records the results obtained on 19 observations in nine patients. In all instances there was obvious dyspnea or evidence of pulmonary congestion, or both. In every case, twenty-four hours after the diuretic was given, definite improvement in the respiratory function

*From the medical service of the Peter Bent Brigham Hospital, Boston.

TABLE I

CASE NO.	MEDICAL NO.	AGE	SEX	DIAGNOSIS	MEDICATION	LUNGS		VITAL CAPACITY		URINE OUTPUT	SUBJECTIVE CHANGE	MISCELLANEOUS NOTES
						BEFORE DIURESIS	AFTER DIURESIS	BEFORE	AFTER			
1	49925	56	M	Hypertensive heart disease	12/2/36 1 c.c. mercupurin	Moderate basal râles.	Bases clear.	2500	2800	2300	Dyspnea much less.	Gallop rhythm and pulsus alternans disappeared.
					12/11/36 1 c.c. mercupurin	A few basal râles.	Bases clear.	2550	——	2800	No dyspnea.	Liver no longer palpable.
	50404 (2nd admission)				2/9/37 1 c.c. mercupurin	Moderate basal râles.	Bases clear.	2100	2500	4300	Dyspnea much less.	Again loss of gallop and pulsus alternans. Enlargement of liver gone.
					2/12/37 1 c.c. mercupurin	Clear.	No change.	2900	3250	2150	No dyspnea.	
2	50247	36	F	Rheumatic heart disease	1 c.c. mercupurin	Slight dullness and diminished breath sounds right base.	Bases clear.	1650	1850	2950	Dyspnea gone.	Patient had no peripheral edema.
3	50203	64	M	Rheumatic heart disease	1/14/37 1 c.c. mercupurin	Moderate basal râles.	Bases clear.	1975	2100	6000	Markedly less dyspnea.	Able now to sleep without sedative.
					1/21/37 1 c.c. mercupurin	Few basal râles.	Clear.	2100	2350	4000	No dyspnea.	
					1/30/37 1 c.c. mercupurin	Clear.	No change.	2150	2275	5650	No dyspnea.	

TABLE I—CONT'D

4	50082	68	F	Hypertensive heart disease	12/20/36 1 c.c. mercupurin	Moderate basal râles with diminished resonance and breath sounds.	Few râles. Less dullness and better quality breath sounds.	1380	——	4235	Dyspnea very much less.	Vital capacity showed steady improvement though peripheral edema returned between each diuresis.
					1/5/37 1 c.c. mercupurin	As after last diuresis.	No râles. Slight dullness at bases.	1650	——	3625	Dyspnea less.	
					1/10/37 1 c.c. mercupurin	As before.	Clear.	——	——	2190	Dyspnea less.	
					1/15/37 1 c.c. mercupurin	Clear.	Clear.	——	1875	2610	No dyspnea.	
5	48164	56	M	Hypertensive heart disease	1 c.c. salyrgan	Moderate basal râles. Slight fluid at right base.	Not recorded.	1600	1800	610+	Less dyspnea.	
6	47057	50	F	Rheumatic heart disease	8/4/35 2 c.c. salyrgan	Numerous basal râles. Slight fluid right base.	Râles less, fluid gone.	——	——	2100	Dyspnea better.	Patient had no cardiac reserve and was in constant failure under ideal bed care.
					1/18/36 mercupurin suppository	Moderate râles, fluid at base.	Râles much less, fluid gone.	1400	1600	3100	Dyspnea better.	
					3/2/36 mercupurin suppository	Moderate râles, fluid at bases.	Râles much less, fluid gone.	——	——	4000	Dyspnea better.	
7	50531	29	F	Rheumatic heart disease	1 c.c. mercupurin	Few râles at both bases, slight dullness.	Clear.	1625	1900 (48 hr.)	1100+	Dyspnea gone.	Patient had no edema.
8	50219	42	F	Rheumatic heart disease	2 c.c. mercupurin	Moderate râles at bases, slight basal dullness.	Clear.	1425	1900	2750	Dyspnea gone.	Liver no longer palpable. Patient had no edema.
9	51172	38	M	Hypertensive coronary disease	1 c.c. mercupurin	Few basal râles. Diminished resonance and breath sounds at right base.	Clear.	2800	3400	6585	Dyspnea gone.	Liver no longer palpable.

took place. This was apparent from the subjective amelioration of the breathlessness and the changes on physical examination of the lungs. The degree of moisture at the bases of the lungs diminished, as evidenced by the absence of râles, the amount of dullness, or the character of the breath sounds. More convincing than the subjective improvement in breathing, which the patients themselves often noticed, was the increase in the vital capacity of the lungs. There were eight patients in whom 12 readings were made before and after a diuresis. The average increase in vital capacity was 290 c.c. The smallest increase was 125 c.c., and the largest was 600 c.c. There were other occasions where a diuretic was given when the vital capacity was not measured, but when improvement in the breathlessness and in the physical findings in the lungs attested to the beneficial effects of the drug. The diuretic effect of the injections was manifested by the prompt and decided increase in the urinary output and the loss of weight which took place during the twenty-four-hour period. The minimum output was 2,150 c.c., the maximum output 6,585 c.c., and the average was 3,319 c.c.

Although this group is small, cases were particularly chosen that did not have massive edema; in fact, most of them had only slight or moderate edema. Of especial importance were those that showed no obvious peripheral pitting. It is in this latter group, which presents the picture of dyspnea without any peripheral edema, that physicians have frequently neglected to use diuretics. We have even seen instances in which the physician resented the suggestion that a diuretic be used because there was no obvious edema. These observations illustrate the beneficial result that may be obtained from diuretics on the distressing symptom of breathlessness entirely apart from the well-known effect on edema.

It may be of some interest to discuss the mechanism by which improvement in respiration may take place following a diuresis. Drinker, Peabody, and Blumgart[6] showed that the artificial production of pulmonary congestion in cats caused dyspnea and increased the volume of blood in the lungs. This is quite comparable to what occurs in congestive failure. Furthermore, Parker and Weiss[7] have shown that the capillaries of the lungs in cases of mitral stenosis are markedly dilated so that red blood cells within the center of the stream have little opportunity to absorb oxygen from the alveoli, whereas in the normal lung red cells pass in single rows, being directly exposed to the alveolar epithelium. They also showed that there was considerable pericapillary edema in these cases. Finally, there is adequate evidence to show that the total blood volume is increased in heart failure and that part of this increase is accounted for by passive congestion in the lungs. In this connection it has recently been shown by Evans and Gibson[8] in edematous dogs that a diuresis is accompanied by a sharp decrease in blood volume. From all this it follows that if a diuretic extracts fluid from the engorged capillary bed of

the lungs, both the amount of the remaining air spaces will increase and the capacity for oxygenation of the blood will improve.

SUMMARY

In a group of nine patients with congestive heart failure in whom breathlessness was an outstanding symptom, the immediate effect of a mercury diuretic on the respiratory mechanism was studied. It was found that the average increase in the vital capacity of the lungs twenty-four hours after the injection was 290 c.c. This was accompanied by a prompt improvement in the subjective symptom of respiratory distress and a decrease in the signs of pulmonary congestion.

It is emphasized that the mercury diuretics have a decidedly beneficial effect in cardiac patients with dyspnea, even in those cases in which there is no peripheral pitting edema.

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ELECTROCARDIOGRAPHIC MANIFESTATIONS AND THE CARDIAC EFFECT OF DRUGS IN VITAMIN B_1 DEFICIENCY IN RATS*

SOMA WEISS, M.D., FLORENCE W. HAYNES, PH.D., AND PAUL M. ZOLL, M.D.
BOSTON, MASS.

IN 1930 Drury, Harris, and Maudsley[1] observed a slowing of the heart rate in rats fed on diets deficient in vitamin B_1. This bradycardia was specific for vitamin B_1 and has since been used as a test for the estimation of the vitamin B_1 content in various substances.[2, 3] Pigeons fed on polished rice also show a bradycardia and in some cases heart block.[4-7] No definite changes in the electrocardiographic complexes in deficient animals have been noted by Drury, Harris, and Maudsley[1] or by Carter and Drury.[5] Méhes and Péter[4] observed slight changes in the electrocardiograms of rice-fed pigeons; i.e., the P-R interval was slightly increased and the S- and T-waves were lower than in normal birds.

In human beriberi patients electrocardiographic changes of varying extent have been reported by a number of observers.[8-13] In a discussion of the literature Feil[14] states that in approximately one-third of the cases with "beriberi heart" "low voltage, notching of the QRS in all leads, high T-waves, changing sign of T with recovery, and changes in the P-R interval (variable) were present." In view of the frequent abnormalities, such as T-wave changes, tachycardia and prolonged Q-T interval, recently observed by Weiss and Wilkins[15, 16] in patients with nutritional deficiency, it was decided to undertake electrocardiographic studies on rats kept on an artificial diet deficient in vitamin B_1, in an attempt to obtain further evidence as to the effects of vitamin B_1 deficiency on the heart and the nature of the changes produced.

METHOD

The following control diet was used:

Modified Osborne and Mendel salt mixture[17]	3.5 per cent
Cornstarch (Duryea)	55.0 per cent
Butter fat	8.5 per cent
Washed casein	18.0 per cent
Dry baker's yeast (Fleischmann's unirradiated)	15.0 per cent

Vitamins A and D were supplied by three drops of cod liver oil daily.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Butter was washed with warm water and centrifuged as described by Bliss and Green.[18] At first, commercial casein was shaken for several hours with 60 per cent alcohol, washed thoroughly with more alcohol and the process was repeated on a second day. Later, washed casein* was used after it had been rewashed somewhat less thoroughly with 60 per cent alcohol. Control rats were kept in good condition for many weeks on this diet.

Rats deficient in vitamin B_1 were kept on the same diet, with the exception that the yeast was autoclaved in the presence of base to remove vitamin B_1. Originally, 100 grams of yeast were mixed with enough 0.1 N sodium hydroxide to make a smooth paste (about 125 c.c.) and autoclaved for one hour at a pressure of 20 pounds, in a pan large enough so that the yeast was less than half an inch thick. After autoclaving, an equal amount of 0.1 N hydrochloric acid was added to the yeast, which was then dried under a fan and ground to a fine powder. After using this yeast for eight weeks it was obvious that the diet contained some B_1. Accordingly, the yeast was treated with 1 N sodium hydroxide (pH 8.5 to 9.0) and autoclaved for six hours at a pressure of 15 pounds. Since some of the symptoms produced by this diet suggested that considerable B_2 was also destroyed, rats were later kept on a diet containing yeast which had been treated with 0.1 N sodium hydroxide and autoclaved (15 pounds pressure) for six hours at pH 7.

The body weight, food intake and electrocardiograms were studied on four control and three fasting rats, as well as on 22 rats deficient in vitamin B_1 whose initial weights varied from 70 to 178 grams. In order to ascertain the influence of muscular exercise, four of the vitamin-deficient animals were kept in revolving wheels. All activity could be recorded automatically by a counting device. After about a week the rats learned to run on these wheels and could at times go more than a mile a day.

Rats were allowed to become deficient and then were given subcutaneous injections of aqueous solutions of synthetic crystalline vitamin B_1 (Merck).† In all except a few cases solutions of vitamin B_1 were freshly prepared. Each rat was made deficient and cured several times in this fashion. The doses of vitamin B_1 given were estimated on the basis of the observation[19] that 0.0025 to 0.005 mg. per day is required to promote growth to maximum weight in rats.

Electrocardiograms were taken on the unanesthetized rats at intervals of from one to a few days throughout the study. During the taking of the electrocardiograms the rat was placed on its back on a board to which its feet were tied. Electrodes consisting of several strands of copper wire were dipped in electrode paste and wound about the legs. If the fur was rubbed with a moist cloth, sufficiently low skin resistance could be obtained. The three standard leads were used and in all records the string was standardized. Most of the records were taken on paper running at a speed of 50 mm. per second, but in a few we used a speed of 100 mm. per second.

In order to throw light on the mechanism by which changes due to vitamin B_1 deficiency are brought about, as well as on the sensitivity of the heart in B_1 deficiency, observations were made on the effects of epinephrine, atropine, or strophanthin on normal and on vitamin-deficient animals. Electrocardiograms were taken at frequent intervals for one to two hours after the administration of the drug. In three of the vitamin-deficient animals the effect of section of the vagi was studied.

*Obtained from A. H. Thomas Co.

†We wish to express our thanks to Merck & Co., Inc., Rahway, N. J., for their courtesy in supplying us with crystalline vitamin B_1.

RESULTS

Heart Rate.—Rats, kept on a diet containing yeast which was autoclaved for six hours at pH 8 to 9, began to lose their appetites and failed to gain weight in about 10 days. As is seen in Fig. 1, in a typical case the heart rate fell gradually in four or five weeks from about 500 to 350 or 400 beats per minute. In control rats, after the first few determinations the heart rate remained practically constant from week to week at approximately 500. Vitamin-deficient rats

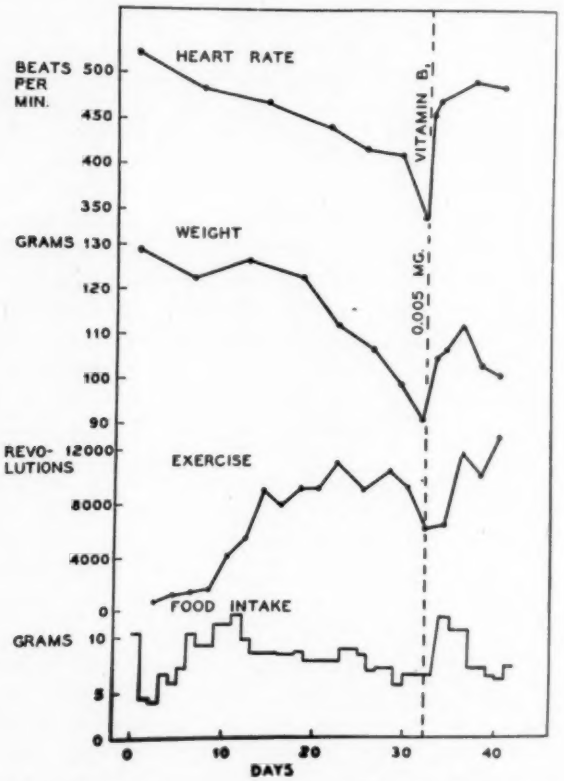

Fig. 1.—Effect of vitamin B_1 deficiency and the injection of crystalline vitamin B_1 on the heart rate, body weight, exercise, and food intake of a rat.

could usually be cured by crystalline B_1 if the rate had not fallen below a level of 350 to 300. When the rats became moribund the rate fell abruptly to from 100 to 200. Drury, Harris, and Maudsley[1] have shown by restricting the food of control animals that the gradual fall in rate to 300 is not due to loss of weight and inanition. We took records on three fasting rats, previously not deficient, in which the rate remained for from three to ten days at about 500 until the day before death, when it fell sharply to from 100 to 200. As previously observed,[1] the rate in vitamin-deficient rats can be raised to practically normal within a few hours with sufficiently large doses of vitamin B_1,

in spite of the fact that food is withheld during this period. Figure 1 shows a case in which the rate rose from 341 to 454 five hours after vitamin B_1, although no food was given. The dose of vitamin administered and the severity of the deficiency determined the number of days before the rate fell again to a dangerous level. Rats can be kept

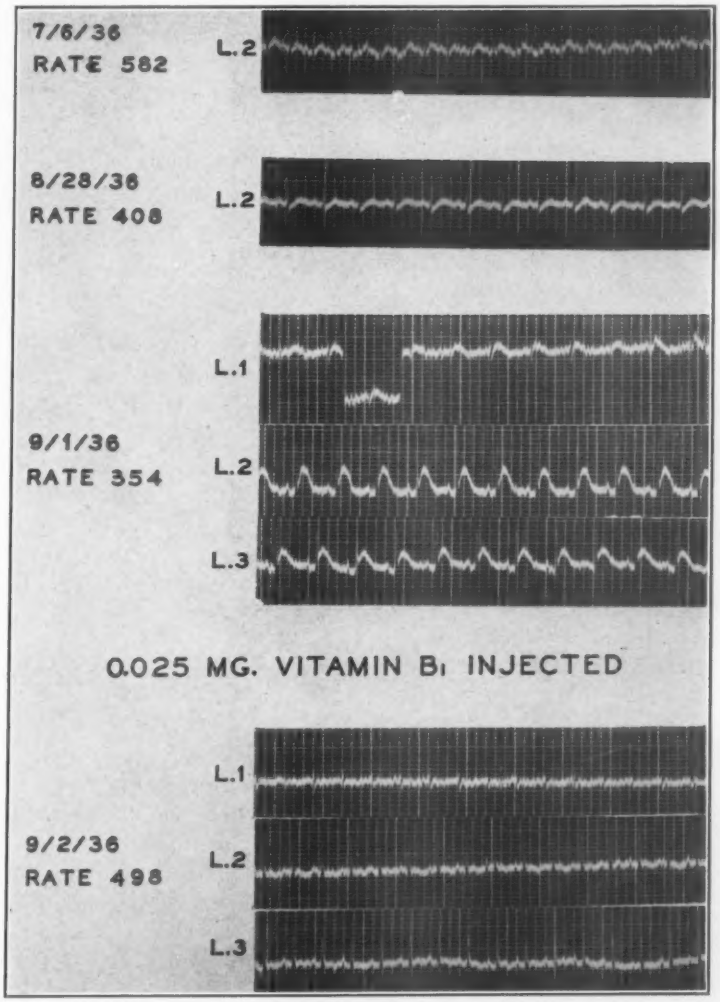

Fig. 2.—Electrocardiograms on a rat fed a diet deficient in vitamin B_1, before and after the injection of crystalline vitamin B_1. The time lines are 1/25 second apart. Note the increase in height of the T-waves on Sept. 1, 1936 and the decrease in height after the administration of vitamin B_1.

in an apparently normal state for long periods on a diet deficient in vitamin B_1 if sufficient crystalline vitamin B_1 is injected.

Electrocardiographic Complexes.—Drury, Harris, and Maudsley[1] did not demonstrate any definite change in the size or the direction of the complexes of their electrocardiograms. Since their records were not

standardized an analysis and comparison of the complexes was not feasible. All but four or five of our series of 22 vitamin-deficient rats showed quite definite changes in the complexes, especially the T-waves, accompanying the decrease in heart rate. In the normal rat electrocardiogram the main deflection as well as the T-waves are upright in

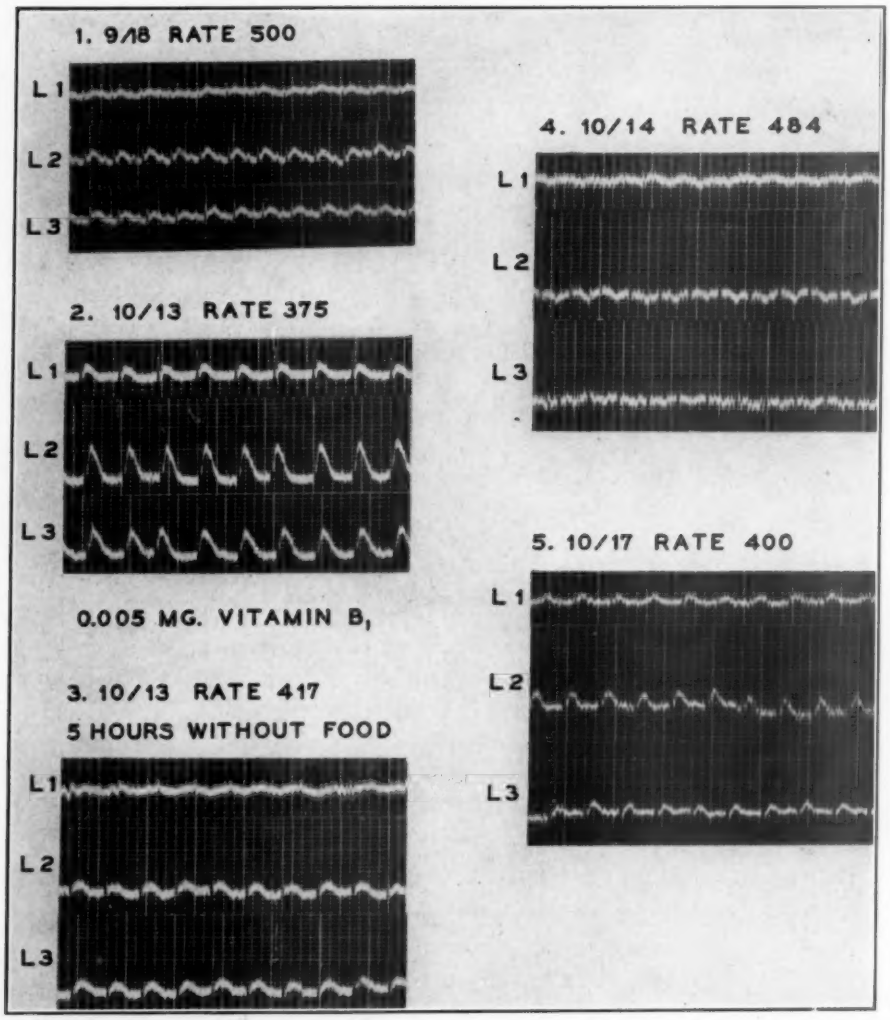

Fig. 3.—Electrocardiograms on a rat fed a diet deficient in vitamin B_1, before and after the injection of crystalline vitamin B_1. The time lines are 1/25 second apart. Note the increased height and the high origin of the T-waves on October 13. Five hours after the administration of vitamin B_1 the T-waves had become lower and within twenty-four hours were inverted.

all leads. Lead I is usually flat, with very small deflections. In our series the main deflection varied between 2 and 8 mm. in normal rats, but as the rats became deficient this gradually increased to from 8 to 16. This did not change to any great extent after vitamin B_1 was injected. The height of T_2 and T_3 normally varied between 0.5 and

2.5 mm. On eight occasions when rats became deficient (with rates between 310 and 410) the T-waves, especially T_2 and T_3, became very high, and on five out of the eight the origin of the T was elevated (Figs. 2, 3, and 4). In the case represented in Fig. 2 the high T-waves disappeared the day after 0.025 mg. of vitamin B_1 was injected, as the

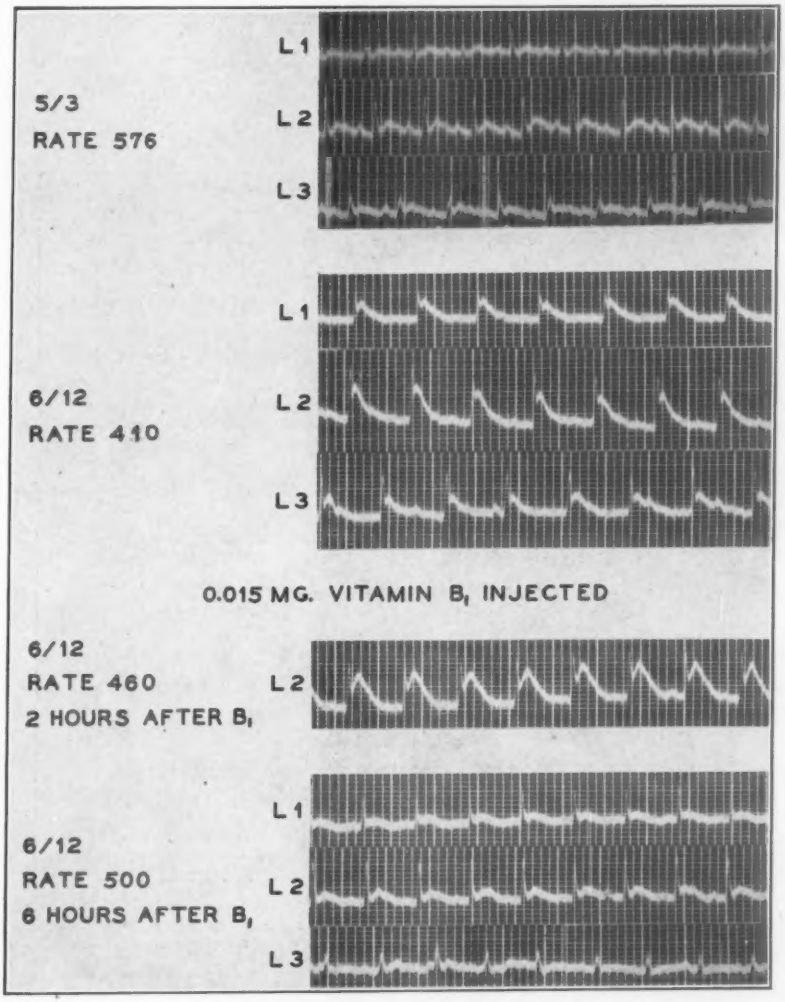

Fig. 4.—Electrocardiograms on a rat fed a diet deficient in vitamin B_1, before and after the injection of crystalline vitamin B_1. The time lines are 1/50 second apart. Note the increased height and the high origin of the T-waves on June 12. Six hours after the administration of vitamin B_1 the T-waves were again practically normal.

rate increased from 354 to 498. In the case shown in Fig. 3, food was withheld for five hours after vitamin B_1 was injected. At this time the T-waves were much lower and the rate had risen from 375 to 417. Food was then given. Eleven hours later the T-waves were inverted and the rate was 484. Three days later the T-waves had again

become upright and normal in size. In another rat, with similar deficiency and a rate of 341, the T-waves became diphasic six hours after vitamin B_1 but without food, and the rate rose to 454. The next day, after food had been given, T-waves remained the same but three days later they were upright and of normal size. Similar temporary disturbances in the T-waves have been observed after the administration of vitamin B_1 and food to vitamin-deficient patients.

In all but two or three instances these high-T-waves were seen the first time the rats became deficient and did not appear subsequently when they were allowed to become deficient with equally low rates.

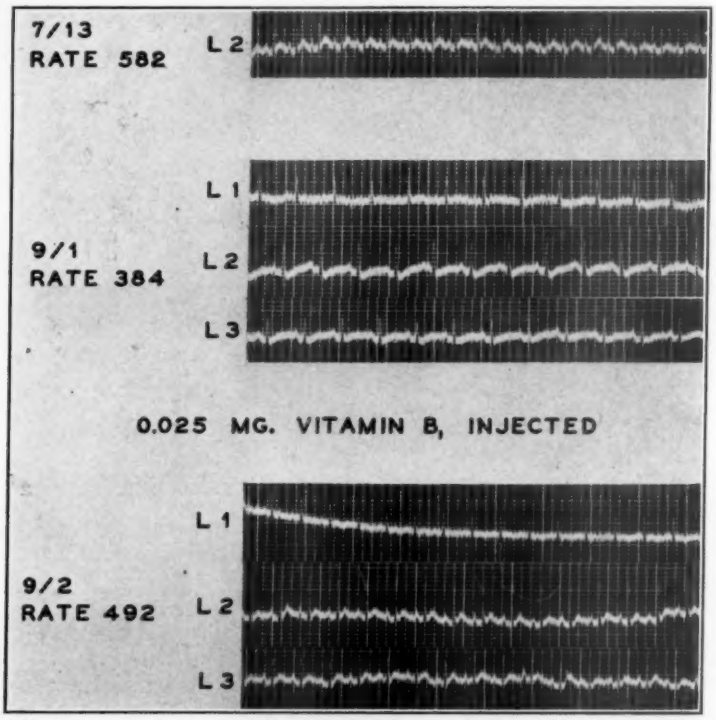

Fig. 5.—Electrocardiograms on a rat fed a diet deficient in vitamin B_1, before and after the injection of crystalline vitamin B_1. The time lines are 1/25 second part. Note the changes in the T-wave on September 1 and its return to normal on September 2.

In many later deficiencies, and in four or more rats the first time they became severely deficient, the T_2 and T_3 became flat or inverted, often with depression of the S-T segment (at rates of from 300 to 430). They usually became upright after vitamin B_1 was given, as is shown in Figs. 5 and 6. The rat represented by Fig. 5 became deficient four successive times with similar changes each time. Occasionally the T became upright while the rate was still low and before vitamin was given, or remained flat when the rate was increased by the injection of vitamin B_1. In the latter instances, however, the doses of vitamin

may not have been large enough to cause prompt changes in the electrocardiogram. In one case T_2 changed from upright to flat with low origin after vitamin B_1 was injected. At certain times rats showed no T-wave changes, although their heart rates fell to the same low levels which had previously accompanied T-wave changes.

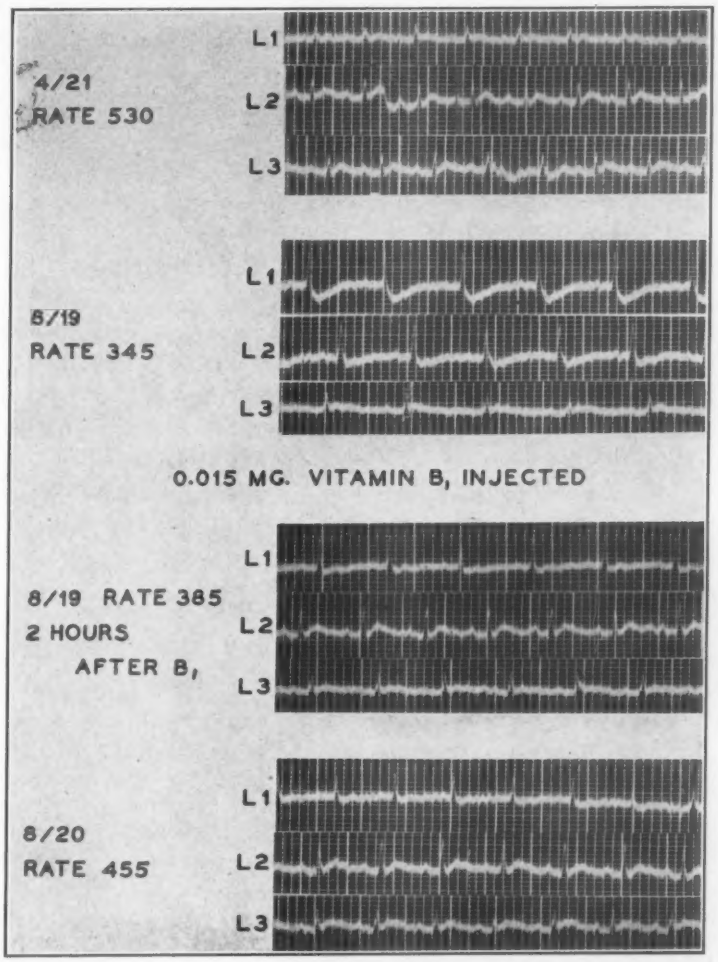

Fig. 6.—Electrocardiograms on a rat fed a diet deficient in vitamin B_1, before and after the injection of crystalline vitamin B_1. The time lines are 1/50 second apart. Note the changes in the T-wave and the depression of the S-T segment on August 19 and the normal complexes after vitamin B_1 was given.

P-R, QRS, and Q-T Intervals.—Our observations confirm those of Drury, Harris, and Maudsley[1] in indicating that although the heart rate falls considerably there is usually no definite change in the P-R or the QRS interval. The speed of the heart rate as well as the presence of somatic tremor often made the records difficult to measure accurately. The P-R interval was lengthened at low rates before death, but in all except four or five cases this set in suddenly and was prob-

ably to be ascribed to the moribund condition of the animal. Previous workers[1] found that the P-wave disappeared at rates somewhat below 350. In only two of our animals did this wave become so low as to be questionable, other rats often showing rates below 350 with definite P-waves. The Q-T interval usually increased as the rats became markedly deficient. The ratio of the Q-T interval to the square root of the R-R interval (K) did not increase as the rate fell and was often somewhat decreased as the rate reached a level of about 400. In fasting rats K increased as the rats became moribund. In many curves the Q-T interval could not be measured in deficient rats because the T-wave did not rise above the isoelectric line.

Exercise.—Only one of the four exercising rats became deficient sooner or showed more marked cardiac changes than the other rats. This may be explained by the fact that they were not forced to exercise and as they became deficient the activity decreased markedly. Cowgill, Rosenberg, and Rogoff[20] have shown that dogs which are forced to exercise develop the anorexia characteristic of vitamin lack faster than other dogs. This would be expected since it has been shown that the vitamin B requirement per unit of tissue mass is proportional to the metabolism of the mass. Figure 1 illustrates the decrease in activity before and the increase after giving vitamin B_1 to a deficient rat. In some cases the deficiency was even more marked.

Epinephrine.—Epinephrine hydrochloride (Lederle) in subcutaneous doses of 0.1 and 0.5 c.c. of 1:10,000 solution per 100 grams of body weight did not consistently affect the heart rate in four controls or five vitamin-deficient rats. In two of the three vitamin-deficient rats receiving 0.5 c.c. the T-waves became somewhat higher in from ten to thirty minutes after epinephrine. The third rat had high T-waves before injection and no change was seen. Sixty to ninety minutes after injection several of the vitamin-deficient rats showed irregularities in rhythm not usually seen in the normal rat.

Atropine and Vagus Section.—Atropine and vagus section had little effect on the rate. Atropine sulfate, administered subcutaneously in doses of 2 to 10 mg. per 100 grams of body weight, produced marked symptoms in each of the six controls and five vitamin-deficient rats tested. There was little if any effect on the rate or the complexes in any of the rats. Two vitamin-deficient rats with flat T-waves and one with high T-waves were given 2 mg. of atropine, but no changes in the complexes were observed. Section of the vagi under local anesthesia was carried out on three vitamin-deficient rats. One rat showed a slight increase in rate and another showed longer P-R and Q-T intervals and lower T-waves after vagus section.

Strophanthin.—The action of strophanthin (Merck) was tested somewhat more extensively in order to determine whether the hearts of vitamin-deficient rats were more sensitive to a "digitalis body" than

those of controls. It is known that rats are resistant to the action of digitalis substances. The subcutaneous doses used were 0.5 and 1 mg. per 100 grams of body weight, the fatal dose for a normal rat being about 2 mg. per 100 grams. Of five control rats given 0.5 mg., three showed a definite decrease in heart rate and the other two slight decreases. Of seven vitamin-deficient rats given the same dose, only

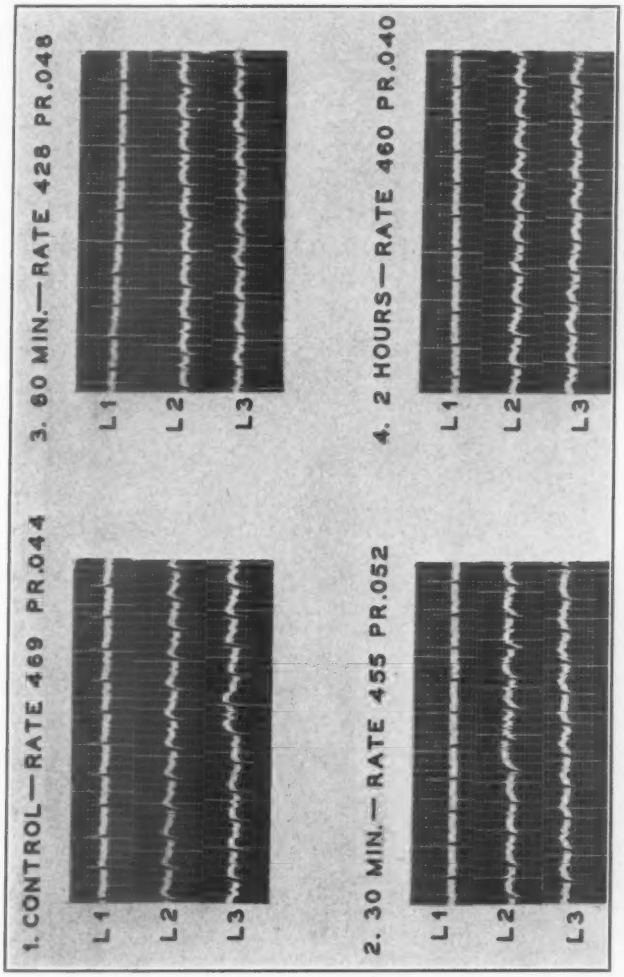

Fig. 7.—Electrocardiograms on a control rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note that the electrocardiogram is essentially unchanged after the administration of strophanthin.

two showed some slight fall in rate. The P-R interval was increased in two controls and two vitamin-deficient rats. The difference between the two groups was seen in the changes in the T-waves. Of the controls receiving 0.5 mg. per 100 grams, only one or two had slightly lowered T-waves in Lead II, and three controls given even larger doses (1 mg.) showed no T-wave changes. Figure 7 presents the records of a typical experiment on a control rat in which the T-waves were not definitely altered. Of the vitamin-deficient rats, however,

four showed a depression of the S-T segment or an inversion of the T-wave. In the experiment represented by Fig. 8, T_2 and T_3 were inverted thirty-five minutes after injection of strophanthin, but gradually returned to upright in the next hour and a half. Figure 9 is the record of another vitamin-deficient rat with a slightly lower initial

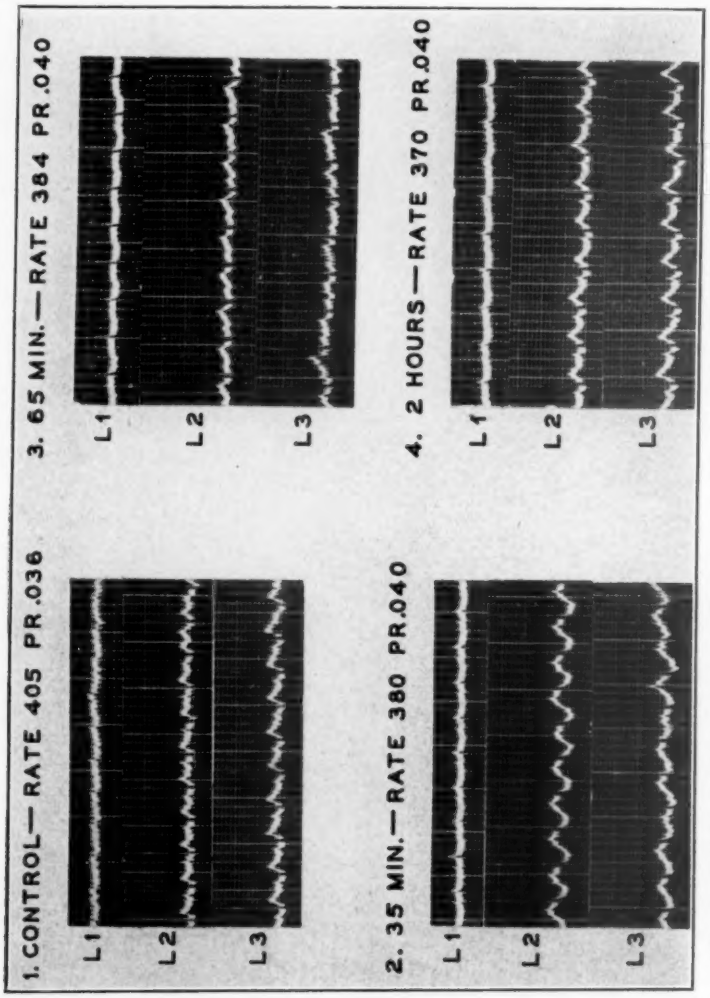

Fig. 8.—Electrocardiograms on a vitamin B_1 deficient rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note the change in the S-T segment 35 minutes after strophanthin.

heart rate (390). In this case T_2 and T_3 became inverted, with progressively lower origin, during a period of two hours after the injection. Two of the vitamin-deficient rats died after one-fourth the fatal dose for normal rats. One of these rats showed high T-waves after strophanthin.

This work is in agreement with previous observations,[21] indicating that the hearts of pigeons fed on polished rice are more sensitive to the effects of strophanthin than those of normal birds. Méhes and

Péter[4] also found a more marked vagal effect after digitoxin in pigeons with beriberi than in normals.

DISCUSSION

As Drury, Harris, and Maudsley have pointed out, the speed with which the rat's heart recovers after the administration of vitamin B_1

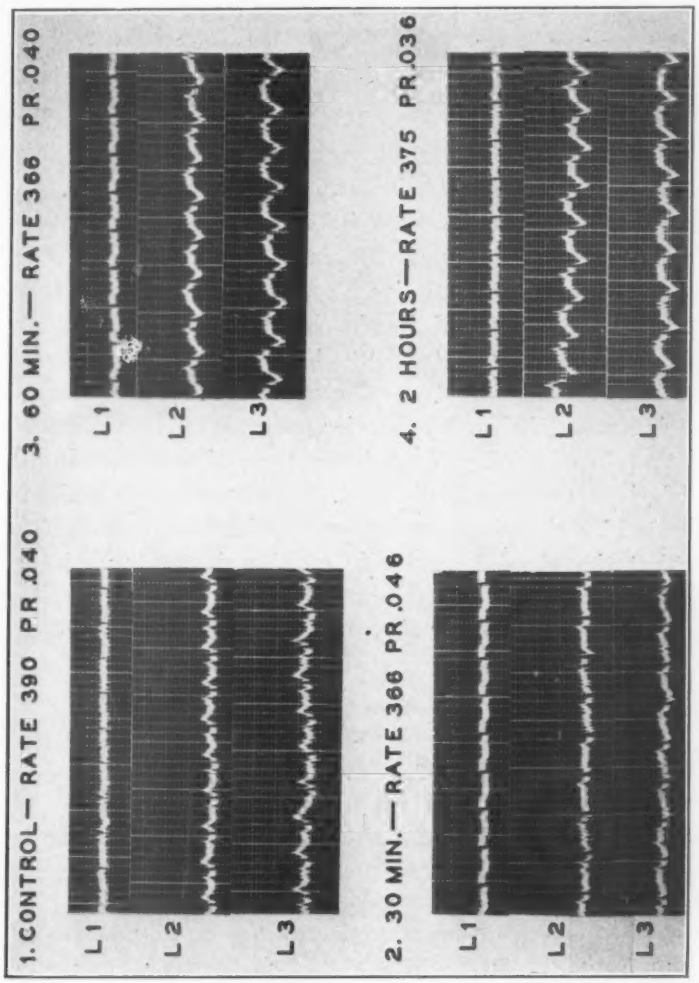

Fig. 9.—Electrocardiograms on a vitamin B_1 deficient rat before and after the subcutaneous injection of 0.5 mg. of strophanthin per 100 grams of body weight. The time lines are 1/25 second apart. Note the progressive changes in the T-waves after strophanthin.

is so great as to rule out an organic degenerative process. If, then, we assume the changes which we have observed to be functional, at least before the deficiency has been very prolonged, they must be explained on the basis of nervous or chemical (hormonal or metabolic) factors, alone or in combination. The bradycardia and heart-block produced in pigeons by feeding them polished rice have been definitely attributed to vagal influence. Carter and Drury[5] conclude that the heart is probably not hypersensitive but that block is the result of

overaction of the vagal centers. In rats the cardiac effects of vitamin B_1 deficiency are apparently not of vagus origin. In man we have demonstrated that the cardiac changes observed in vitamin B_1 deficiency depend in part on myocardial changes, and in part on changes in the vagus system.[15, 16] Hypertrophy of the suprarenal gland observed in rats and pigeons with vitamin B_1 deficiency[22, 23] has been mentioned[1] as bearing on the cardiac effects of the deficiency, but no definite relationship has been found and the issue is confused by the effects of inanition.[24]

Considerable emphasis has been laid on the metabolic effects of vitamin B_1 deficiency. A number of abnormalities of the carbohydrate metabolism have been reported, including the lowering of the respiratory quotient[25] and the increase in the glycogen content of the liver[26] in polyneuritic pigeons, the accumulation of lactic acid in the blood of rats[2] as well as in the muscle, liver, and heart,[27] and the accumulation of pyruvic acid in the blood of pigeons and rats.[28] Birch and Harris[2] have pointed out that the defect in lactic acid metabolism is a consistent feature of vitamin B_1 deficiency in various tissues and is present in various species. Inawashiro and Hayasaka[29] concluded that lack of vitamin B leads to a disturbance in the resynthesis of glycogen from lactic acid. The removal of lactic acid is also accelerated by vitamin B. From such evidence Birch and Harris[2] suggested that the physiological rôle of vitamin B_1 is to intervene, in a capacity corresponding with that of coenzyme, at some stage in carbohydrate metabolism involving the formation and oxidation of lactic acid. They stated that from what is known of the influence of lactic acid on heart rhythm it is to be expected that an excess will diminish the rate of beat in vivo as it does in isolated preparations. Their attempts to influence the rate by the administration of large doses of calcium lactate, however, have been unsuccessful.

More recently Birch and Mapson[30] have suggested that the bradycardia in rats and possibly also the disturbed carbohydrate metabolism are due to the accumulation of adenylic acid through failure to convert it into innocuous products.[31] The relation of lactic, pyruvic, and adenylic acids to the cardiac effects of vitamin B_1 deficiency in rats will be discussed in a subsequent communication.

SUMMARY

1. An analysis has been made of the cardiac rate, electrocardiographic complexes, and the response to drugs of rats in the nondeficient state and in repeatedly induced vitamin B_1 deficiency.

2. The heart rate of rats on a diet deficient in vitamin B_1 fell gradually to a level of from 350 to 300 beats per minute, from which it could

usually be returned to approximately the normal level (450 to 500) within a few hours by adequate doses of crystalline vitamin B_1, even if food was withheld.

3. In all but four or five of the 22 vitamin-deficient rats studied, the decrease in heart rate was accompanied by changes in the electrocardiographic complexes, consisting most frequently of an increase in height, flattening, inversion, or high or low take-off of the T-waves and depression of the S-T segment. With the doses of vitamin B_1 used the T-waves usually returned to normal within from several hours to a day, although occasionally several days were required. The changes in the electrocardiographic complexes had no close relation to the level of the heart rate, and were not identical in the same animals on successive deficiencies.

4. With the exception of very low cardiac rates the P-R interval remained essentially unchanged. The ratio of the Q-T interval to the square root of the R-R interval (K) usually did not increase as the cardiac rate decreased.

5. Only one of four rats which were allowed to exercise on running wheels became deficient sooner than other vitamin-deficient animals. In none of the four exercising rats were the cardiac changes more marked or of different character than those found in the control vitamin-deficient rats.

6. The cardiac responses of normal and vitamin-deficient rats to epinephrine were essentially the same. Occasional irregularities were observed in the vitamin-deficient animals.

7. Atropine and section of the vagus nerves did not abolish the cardiac slowing or the electrocardiographic changes produced by vitamin B_1 deficiency.

8. The vitamin-deficient rats were more sensitive to the toxic effects of subcutaneous doses of strophanthin, and depression of the S-T or inversion of the T-wave supervened with doses which caused no change in normal rats.

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EXTRA SOUNDS OCCURRING IN CARDIAC SYSTOLE*

FRANKLIN D. JOHNSTON, M.D.
ANN ARBOR, MICH.

DURING the last five years we have seen a number of patients who have displayed on auscultation a distinct sound occurring in cardiac systole. The character of this sound varied somewhat, but in most instances it was of such short duration that it could best be described as a click. The extra sound frequently gave rise to a gallop rhythm, which, in a few cases, had been confused with the more common type of gallop where the third sound occurs in diastole. Although few reports regarding systolic gallop rhythm are to be found in the literature, Macleod, Wilson, and Barker,[1] Wolferth and Margolies[2, 3] and White[4] have briefly discussed the condition and have agreed that its presence has no unfavorable prognostic significance. Gallavardin,[5] Lian and Deparis[6] and a few other workers in Europe have reported a number of cases with clicking sounds in systole. On the basis of three autopsied cases where pleuropericardial adhesions were found these observers[5, 6] believe that the clicks may arise from the presence of delicate strands joining pericardium and pleura. Thompson and Levine[7] have recently published a clinical study of 35 patients displaying systolic gallop rhythm. They pointed out that the condition is not rare since it occurred in 16 per cent of all patients with gallop rhythm encountered over a period of eleven years. They emphasized further that organic heart disease is usually absent in these patients and that systolic gallop rhythm does not indicate a bad prognosis. It is the purpose of this paper to present a study of 21 cases of systolic gallop rhythm studied by means of sound tracings.

METHODS

In addition to clinical examination of the heart, standard electrocardiograms and x-ray studies of the heart and lungs were made whenever such examinations were possible. All patients were examined by a member of the heart station staff and the diagnosis of systolic gallop rhythm was made or confirmed by auscultation before sound tracings were taken.

Two Einthoven string galvanometers arranged in tandem were employed to record an electrocardiogram, usually standard Lead I, simultaneously with the sound tracing. A condenser microphone arranged in the manner described in a recent communication from this

*From the Department of Internal Medicine, University of Michigan Medical School.
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TABLE I

CASE NO.	AGE	SEX	DIAGNOSIS	CARDIAC SYMPTOMS	PHYSICAL FINDINGS	X-RAY	ELECTROCARDIOGRAM
1	5	M	Cleft lip and palate.	None.	Inconstant systolic gallop at apex. Rough systolic murmur at pulmonic area.	Normal heart and lungs.	Normal.
2	12	M	Rheumatic heart disease with aortic insufficiency.	Pain like pin pricks over heart.	Loud systolic gallop at apex. Faint aortic diastolic murmur.	Normal orthodiagram. Some calcification of hilar nodes.	Normal.
3	15	F	? Rheumatic fever. Neurasthenia.	None.	Tachycardia. Transient extra sound heard best inside apex only in deep inspiration. Blood pressure 118/70.	? active tuberculosis at right apex. Slight hilar calcification.	Normal.
4	17	F	Chronic septic arthritis, left hip.	None.	Systolic click loudest at apex. No cardiac enlargement. Blood pressure 118/68.	--------	P-R interval 0.22.
5	18	F	Psychoneurosis. Hysteria.	Some pain over heart. Tachycardia.	Systolic click at apex, disappears on deep inspiration. Blood pressure 118/90.	Small drop type heart. Lungs normal.	--------
6	19	F	Chronic pelvic inflammation (gonococcal).	None.	Click associated with short systolic murmur loudest inside apex. Blood pressure 110/80.	--------	--------
7	19	F	Acne vulgaris. Undernutrition.	None.	Systolic click at apex varying markedly with respiration. Blood pressure 120/70.	Orthodiagram and chest stereoroentgenogram, negative.	--------
8	20	F	Congenital absence of genital organs.	None.	Late systolic click and murmur at apex. Blood pressure 138/80.	Prominent conus. Hypoplastic aorta. Slight calcification of hilar nodes.	Flat T's. (digitalis).
9	23	F	No disease.	None.	Click at apex which disappears on deep inspiration and when patient sits up.	Old parenchymal scarring. Slight calcification of peribronchial nodes.	Normal.
10	27	M	Anxiety neurosis.	Palpitation and dyspnea on exertion.	Loud click at apex which disappears on deep inspiration. Blood pressure 145/75.	No cardiac enlargement. Slight peribronchial calcification.	--------
11	28	M	Duodenal ulcer.	Slight dyspnea on exertion.	Highly variable systolic click at apex. Blood pressure 110/60.	Elongation of aorta. Slight tenting of left diaphragm. Slight calcification of hilar nodes.	--------

TABLE I—CONT'D

12	28	F	Hay fever. Asthma.	None.	Fairly loud click at apex. No enlargement of heart or murmurs. Blood pressure 120/75.	--------	--------
13	31	F	Psychoneurosis. Pylorospasm.	None.	Systolic click loudest at apex. No cardiac enlargement. Blood pressure 110/70.	--------	--------
14	31	M	Psychoneurosis.	Pain over heart not suggesting angina pectoris.	Click loudest at apex with patient sitting up, and markedly influenced by respiration. Blood pressure 138/80.	Normal heart and lungs.	Normal except for T's. (digitalis).
15	41	F	Uterine fibroid. ? previous tuberculous infection.	None.	Loud systolic click at apex. Extrasystoles. Blood pressure 120/50.	Borderline sized heart. Slight peribronchial calcification	Ventricular extrasystoles. Otherwise normal.
16	41	M	Cardiac neurosis.	Pain over heart not like angina pectoris.	Click loudest inside apex. Disappears when patient sits up. Blood pressure 105/84.	Heart not enlarged. Aorta long and tortuous. Moderate calcification of hilar nodes.	Normal.
17	48	F	Hypertensive heart disease. Complete A-V heart block.	Some palpitation and dyspnea on exertion.	Moderate cardiac enlargement. Bradycardia. Apical click heard best on inspiration and much louder with patient sitting up. Blood pressure 160/100.	Tortuous aorta. Lungs normal.	Complete A-V heart-block.
18	51	F	Duodenal ulcer. Renal ptosis bilateral.	None.	Click loudest inside apex. Fainter on inspiration but not greatly influenced by change of position. Blood pressure 110/70.	Heart and lungs normal.	Normal.
19	51	F	Menopause	Slight dyspnea on exertion.	Clicking sounds in systole loudest at apex. Blood pressure 145/90.	Heart not enlarged. Elongation of aorta and calcification of bronchial nodes.	--------
20	67	F	Arteriosclerotic heart disease.	Dyspnea on exertion. Palpitation and slight edema of ankles.	Systolic gallop at apex. Moderate cardiac enlargement. Extrasystoles. Blood pressure 130/70.	--------	Ventricular extrasystoles.
21	71	F	Arteriosclerotic and hypertensive heart disease.	Dyspnea on exertion.	Slight cardiac enlargement. Systolic click loudest inside apex. Extrasystoles. Blood pressure 194/106.	--------	Slight left axis deviation.

laboratory[20] was used to take about one-third of the records presented in this series. A crystal vibration pickup* working into a two stage amplifier was employed for the remainder.

Graphic records of the heart sounds furnish objective proof that the extra sounds in question occurred in systole. Further information can be gained by measuring the time intervals separating the peak of the R-wave of the electrocardiogram from the onset of the heart sounds and from the beginning of the extra sound. The measurements given in the article were made with the Lucas comparator. At least four cycles were measured in each instance.

RESULTS

Table I gives in condensed form certain clinical data pertaining to the patients studied. The cases have been arranged according to the age of the patient, which varied from five to seventy-one years. Half of the subjects were in the second or third decade of life and two-thirds were under thirty-five years of age. Fifteen of the 21 patients, nearly three-quarters, were women. The preponderance of women is probably accidental, since over one-half of the patients studied by Thompson and Levine were males.

A wide variety of clinical diagnoses were made on the patients making up the group. The most frequent diagnosis was psychoneurosis or some form of functional nervous disturbance. This was present in six patients (Cases 3, 5, 10, 13, 14, and 16). Organic heart disease was found in four (Cases 2, 17, 20, and 21), but only the last three had cardiac enlargement or symptoms that indicated myocardial weakness. Arterial hypertension was present in two cases (17 and 21). Lian and Deparis mention that pain over the heart was a frequent complaint of their patients with systolic gallop rhythm, and suggest that pleuropericardial adhesions may explain the pain as well as the abnormal sound. Four of our patients complained of precordial pain (Cases 2, 5, 14, and 16) but three of these had psychoneuroses which made the symptom difficult to evaluate.

In all of our patients the systolic click was of maximal intensity at, or a short distance medial to, the cardiac apex, although in many of them it could be heard faintly at the base of the heart. The loudness of the extra sound varied greatly from patient to patient as will be seen by inspection of the curves shown in Fig. 1. Of greater significance was the change in the loudness of the click in a given subject with respiration or shift of position. This variation, usually far greater than coincident changes in the loudness of the heart sounds, was never

*The crystal pickup consists of a slab of especially prepared Rochelle salt crystal supported in a suitable housing so that vibrations from the chest wall are transmitted to the crystal. Voltages proportional to the frequency and magnitude of the mechanical vibrations appear on the faces of the crystal. These small differences of potential, amplified by vacuum tubes, may be recorded by the string galvanometer or other means. The crystal pickup used was designed and built by Mr. G. Howlett Davis.

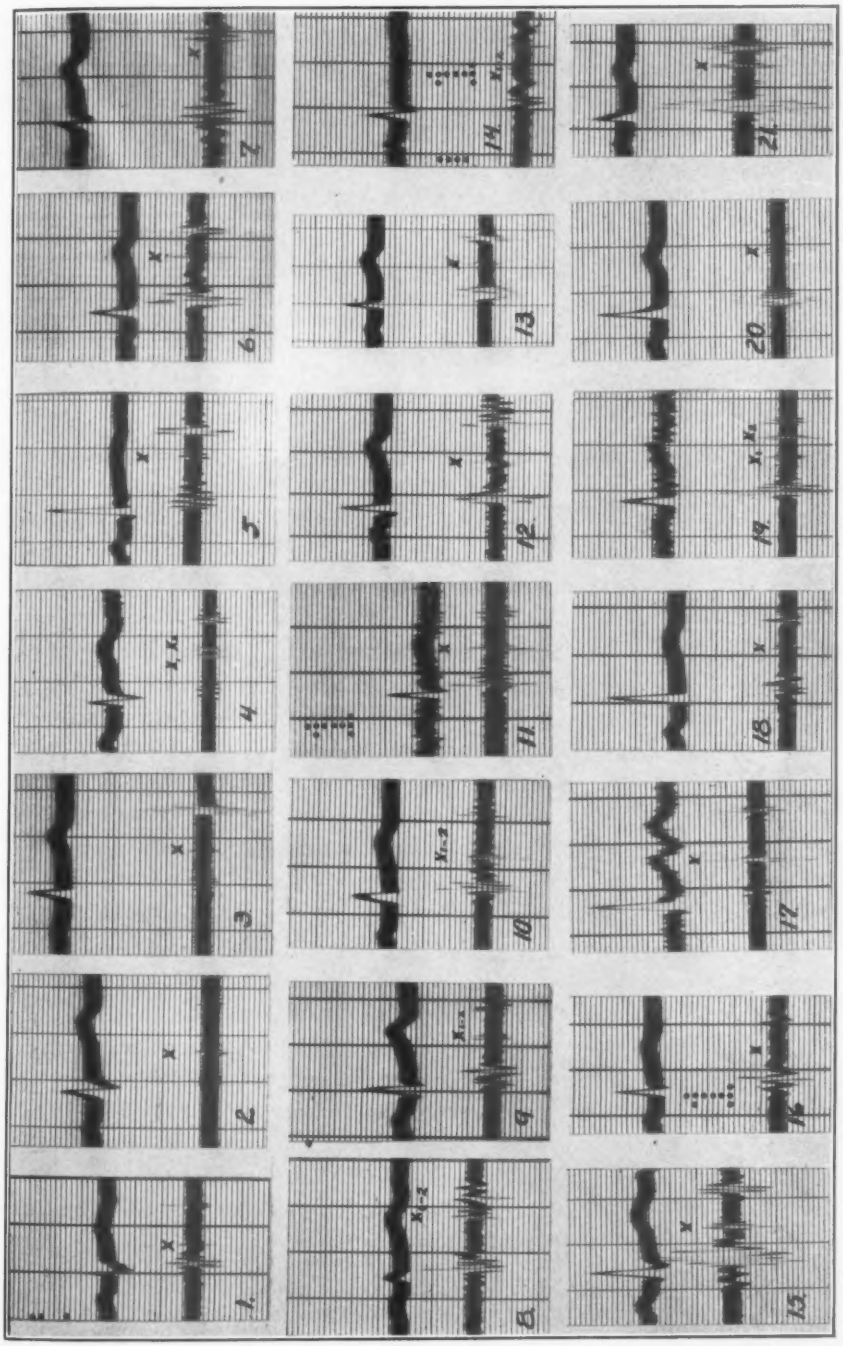

Fig. 1.—The curves corresponding to the cases that were studied (Table I) are arranged consecutively with the case number in the lower left hand corner of each figure. In all figures standard Lead I is the upper curve while the sound tracing taken at or just inside the cardiac apex is the lower curve. The extrasystolic sounds are labeled with an X or when two such sounds were present by X_1 and X_2 or $X_{1\text{-}2}$.

absent when it was specifically looked for. Our clinical notes are incomplete in this respect, but in nine cases a relation between the loudness of the extra sound and respiration or position was noted. In four patients (Cases 5, 9, 10, and 18) the click diminished or disappeared entirely with deep inspiration, while in two others (Cases 3 and 17) the sound was accentuated during inspiration. In two instances (Cases 9 and 16) the extra sound disappeared when the patient sat up, while in two others (Cases 14 and 17) it was loudest with the subject erect.

In addition to the changes in the loudness of the systolic click under different circumstances it was possible occasionally to detect by auscultation that it shifted its position in systole from cycle to cycle. This variation was exhibited to a high degree by Case 1 and is illustrated in Fig. 2*A* where several heart cycles are reproduced. This subject is discussed more fully in a later section of this article.

It became clear early in the progress of this study that, while the systolic clicks were intimately associated with the motion of the heart, they were probably extracardiac in origin and it was hoped that x-ray studies of the heart and lungs might help to explain their presence. Such examinations were available in fifteen of the cases and the results are included in Table I. Although nine patients had slight to moderate calcification of the peribronchial lymph nodes and one slight tenting of the left diaphragm, no clear-cut evidence of pleuropericardial adhesions was found. Elongation or tortuosity of the aorta or both were found in four subjects. Standard electrocardiograms were taken in thirteen of our cases. Six of these were normal. One showed complete A-V block (Case 17). The remainder showed miscellaneous minor abnormalities, which are listed in the last column of Table I.

Referring to Fig. 1 we see that in five of the patients (Cases 1, 2, 10, 15, and 16) the extra sound was definitely in early systole while in six others (Cases 5-8, 20, and 21) it was late systolic in time. The click occurred nearly in midsystole in nine subjects (Cases 3, 4, 9, 11-14, 17, and 18). In one instance (Case 19) two clicks were constantly present, one in early and the other in late systole. In the majority of the records, from sixteen patients, the extra sound is represented by a series of vibrations lasting not more than 0.03 second. The click in the remaining five patients (Cases 4, 8, 9, 10, and 14) was more or less widely split into two components. In Case 6 the click was followed by a short systolic murmur.

If the clicks under consideration are extracardiac in origin they might be expected to show a greater variation in time with respect to a fixed point of the accompanying electrocardiogram than either the first or second heart sound. Since the exact onset of the first sound is often uncertain, the measurements included in Table II com-

pare the interval between the peak of the R-wave and the beginning of the extra sound with the interval between the peak of the wave and the beginning of the second sound. To demonstrate the relative

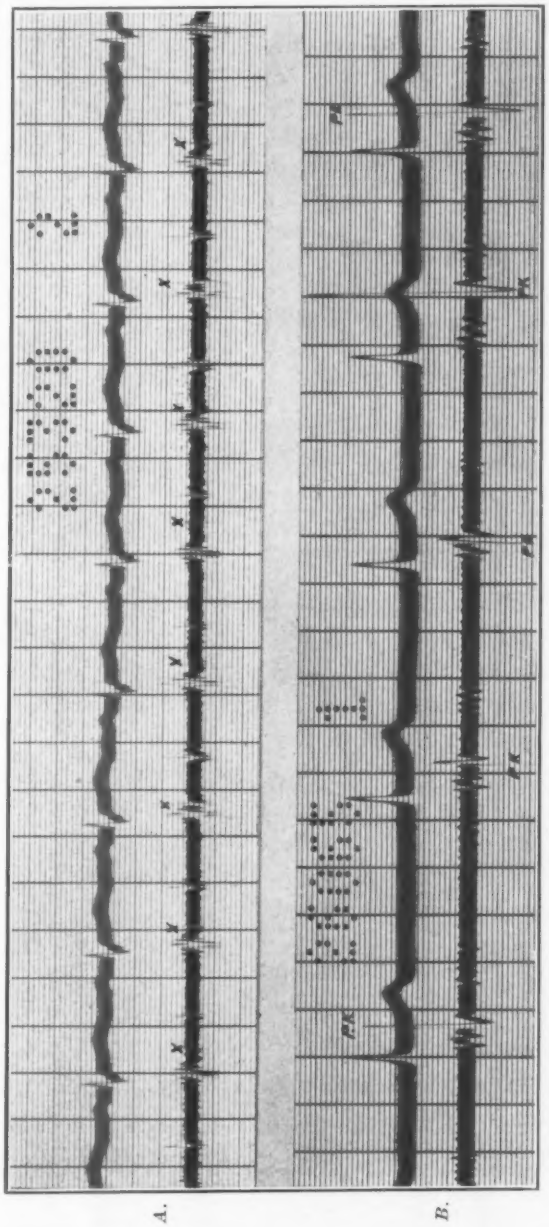

Fig. 2.—The upper curves, Fig. 2A, show eight complexes from Case 1. The position of the extrasystolic sound, labeled *X*, is highly variable. The lower curves, Fig. 2B, show a "pericardial knock" labeled *PK*, occurring at different points of systole (see text).

degree of variability between these two sets of measurements the coefficient of variation (defined as the standard deviation divided by the arithmetic mean) has been determined for both sets of measurements. The cases are arranged in Table II according to the magnitude

TABLE II

CASE NO.	NUMBER OF COMPLEXES MEASURED	AVERAGE TIME FROM		STANDARD DEVIATION		COEFFICIENT OF VARIATION	
		PEAK R TO EXTRA SOUND SECOND	PEAK R TO SECOND SOUND SECOND	R-X	R-SECOND	R-X	R-SECOND
1.	6	0.129	0.283	0.031	0.004	0.242	0.015
2.	4	0.157	0.377	0.025	0.005	0.162	0.012
17.	6	0.215	0.399	0.028	0.017	0.129	0.043
5.	4	0.198	0.320	0.016	0.003	0.081	0.009
11.	4	0.219	0.342	0.017	0.004	0.077	0.011
19.	4	0.176	0.329	0.012	0.007	0.069	0.021
9.	8	0.236	0.352	0.014	0.003	0.058	0.009
6.	10	0.226	0.335	0.011	0.003	0.050	0.009
21.	5	0.264	0.320	0.013	0.001	0.049	0.003
12.	7	0.211	0.380	0.009	0.005	0.045	0.013
16.	6	0.187	0.297	0.008	0.003	0.041	0.011
3.	8	0.181	0.341	0.007	0.004	0.039	0.012
15.	10	0.176	0.335	0.007	0.008	0.038	0.024
20.	5	0.247	0.343	0.009	0.002	0.036	0.005
18.	8	0.206	0.313	0.007	0.004	0.035	0.013
10.	6	0.156	0.343	0.005	.0001	0.033	0.004
13.	8	0.215	0.339	0.006	0.003	0.028	0.009
8.	4	0.245	0.327	0.006	0.001	0.023	0.003
4.	7	0.203	0.353	0.004	0.003	0.020	0.009
14.	5	0.173	0.293	0.003	0.001	0.018	0.003
7.	6	0.304	0.368	0.004	0.002	0.013	0.007

of the coefficient obtained from the measurements which gives the position of the extra sound. It is apparent that the position of the extra sound in the cardiac cycle was much more variable in some cases than in others. The coefficient mentioned varies from 0.242 in the first case (Case 1) to 0.013 in the last (Case 7). This coefficient is, however, uniformly larger than that based on measurements of the second sound. It will be seen that in each case the latter is smaller than the former. It is evident then that in all of the cases the systolic click was more variable with respect to the peak of the R-wave of the electrocardiogram than was the second heart sound.

DISCUSSION

The results presented confirm the opinion formed by other workers that systolic gallop sounds usually occur in patients who show no evidence of organic heart disease and that they have no unfavorable prognostic significance. Although we have no accurate figures on the subject we believe with Thompson and Levine that systolic gallop rhythm is relatively common and that its only clinical importance lies in the fact that it may be confused with diastolic gallop rhythm. One of our patients (Case 14) is a case in point. In this instance the presence of a systolic click had led on a previous occasion to the diagnosis of a serious heart condition and, as a result, the patient had developed a cardiac neurosis which proved very difficult to treat.

The mechanism responsible for the production of extrasystolic sounds is not known. It has been mentioned that Gallavardin and also Lian and Deparis believed the clicks might be due to the presence of pleuropericardial adhesions. Thompson and Levine have referred to two other theories which have been advanced to account for the occurrence of extra systolic sounds. The first, supported by Obrastzow,[8] Bard,[9] Giroux[10] and others, presupposes a lengthening of the period of isometric contraction of the ventricle with separation of the elements that usually blend in the normal first heart sound, while the second, proposed by Potain[11] and supported by Wiedemann,[12] assumes that distension of an atheromatous aorta can produce the sounds in question. The last of these theories does not adequately explain the occurrence of the clicks in two-thirds of our patients who were under thirty-five years of age and in whom there was no reason to suppose that disease of the aorta could be a significant factor. Furthermore it is not likely that sounds arising in the aorta would be heard with maximal intensity in the region of the cardiac apex or that the loudness of such sounds would be greatly influenced by the position of the patient or by respiration. It is also difficult to understand how systolic clicks can be produced by separation of the elements of the first sound due to abnormal lengthening of the period of isometric contraction. Such lengthening implies an abnormal weakened myocardium, a condition notably absent in the great majority of our patients. Assume, however, for the moment that this difficulty is removed and that the valvular element of the first sound may be delayed enough to be separate from the muscular element. Under these circumstances, an extra sound in early systole, such as was present in five of our patients, might occur but in the remainder of our cases the click was placed primarily in mid or late systole and in these the theory is not tenable.

Margolies and Wolferth have discussed briefly a rare type of systolic gallop rhythm which is heard best at the base of the heart and appears to have the ominous prognostic significance usually associated with diastolic gallop rhythm. None of our cases fit into this group but it is possible that in some of the patients investigated by previous workers, particularly Potain and Wiedemann, the gallop was of this type.

All the evidence both from their clinical characteristics and from the measurements showing the great variability with which the clicks appear in systole indicates that they arise outside of the cavities of the heart and are not dependent upon intraventricular or intra-aortic pressure changes as are the heart sounds and murmurs. It is also apparent that they are in some way produced by the motion of the heart and, since they are so markedly influenced by respiration and the position of the patient, it is difficult to escape the conclusion that the clicks arise from the motion between the pericardium and the

mediastinal or diaphragmatic pleura. We thus return by a somewhat roundabout process of exclusion to the theory that the clicks are due to pleuropericardial adhesions, or to some other anomaly of these structures which allows vibrations to be produced in systole. None of our cases have come to autopsy and the only direct evidence supporting the theory is found in the three autopsied cases of Gallavardin. It is hoped that as time goes on more post-mortem evidence will be available so that the theory can be definitely accepted or rejected. It is possible that roentgen kymographic studies may help to solve this problem.

Before closing this discussion the possible relationship between systolic clicks and the so called "pericardial knock" heard occasionally after spontaneous or traumatic left pneumothorax or during the therapeutic induction of left pneumothorax should be mentioned. These sounds may be loud enough to be heard by an observer across the room from the patient who may be unable to rest because of them. They have been described and explained in different ways by several authors including Rees and Hughes,[13] Smith,[14] Munden,[15] Hull,[16] Lister,[17] and Wolferth and Wood.[18] These knocks have many features in common with systolic clicks. They are best heard in the region of the cardiac apex, are strikingly influenced by respiration and by position, vary greatly in intensity from time to time, and are sharp short sounds synchronous with the heart beat. Barnwell and Greene[19] have studied a number of patients where the sound occurred during the induction or maintenance of left pneumothorax and believe that the knocks are produced by a highly active heart whose movements are not limited or cushioned by lung tissue either striking the chest wall or the diaphragm held tense by an air containing viscus beneath. It is not certain whether these pericardial knocks always occur in systole but sound tracings with a simultaneous electrocardiogram have been taken from two patients displaying the phenomenon and in both of them the sound occurred in systole. Figure 2*B* shows one of these records and it will be observed that the knock is represented by vibrations of very large amplitude occurring in different parts of systole.

CONCLUSIONS

Clinical studies on a group of 21 patients displaying systolic gallop rhythm confirm the generally accepted opinion that extra sounds of this type usually occur in the absence of organic heart disease and that their only importance lies in the fact that they are occasionally mistaken for diastolic gallop sounds.

Sound tracings recorded simultaneously with the electrocardiogram were taken on all the patients of the series. Measurements made on these curves indicate that the position of the extra sounds in systole is usually much more variable than is the position of the second sound

with respect to a fixed point of the accompanying electrocardiogram. These results together with the clinical characteristics of the sounds indicate that they are extracardiac in origin. Similarities between systolic clicks and the pericardial knocks heard occasionally in patients with left pneumothorax are pointed out.

The writer wishes to express his appreciation to Dr. Frank N. Wilson for his many suggestions and for his help, particularly in the preparation of this paper.

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A NOTE ON PERICARDIAL INVOLVEMENT IN CORONARY THROMBOSIS*

CHARLES F. STEWART, A.B., AND KENNETH B. TURNER, M.D.
NEW YORK, N. Y.

THE common conception of the pericardial lesion associated with coronary thrombosis and myocardial infarction is that, when present, it consists of a localized patch of fibrinous exudate overlying the infarcted area. Thus Levine[1] states, "When the process of infarction is sufficient to extend from within the ventricle to its surface, the pericardium is necessarily involved. At this point, a localized fibrinous exudate develops and therefore a true serofibrinous pericarditis will result. It is obvious that if the infarction does not extend to the visceral pericardium, no pericarditis occurs; or if the site of the lesion is in the posterior part of the heart or over the dome of the diaphragm even if the pericardium is involved, a friction rub might not be audible. . . . Only on very rare occasions is pericardial effusion associated with this type of pericarditis."

Similarly Levy[2] says, "With the formation of an area of infarction involving the epicardial surface, pericarditis develops and a friction rub may be heard. . . . It is heard in a minority of cases. If the infarct is on the posterior aspect of the heart, the rub is not audible. . . . I have never observed effusion in detectable amount associated with the pericarditis of infarction; it has been reported in rare instances. In a few hearts examined at necropsy, adhesions between the two layers of the pericardium in the region of the infarct have been found."

White[3] states, "Pericarditis due to infarction is usually limited to the area of necrosis in contradistinction to the general involvement of the pericardium by infection."

On the other hand, Blumer[4] states that "a usually localized and usually transitory pericarditis is clinically demonstrable in a certain proportion of patients with coronary occlusion, possibly in a third of them. Occasionally much more widespread pericarditis is present, which may involve the entire pericardial sac and eventually lead to its obliteration." The experience in this hospital is in accord with this view.

Sixty cases of coronary thrombosis examined at necropsy form the basis of this report.† In 12 of these the pericardium was normal, while in 48 (80 per cent) pericardial involvement was demonstrated. In the group with pericarditis, the process was localized to the region

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

†The authors wish to express their appreciation to the Department of Pathology (Dr. J. W. Jobling, Director) for permission to utilize the autopsy records and in particular to Dr. W. C. von Glahn, for his assistance in reviewing the post-mortem findings in the cases here reported.

of the infarct in 36 (75 per cent) and was generalized so that it involved the whole pericardial surface in 10 (21 per cent). It was generalized, but complicated by, and possibly due to uremia in 2 (4 per cent).

Of the 36 cases of localized pericardial involvement there was a healed fibrous patch or adhesion with an old infarct in 21. Such a lesion would not be expected to cause a rub and none was heard. In 15 cases the infarction was recent and an area of localized, acute fibrinous pericarditis was present. This occurred in the apical region or on the anterior surface of the heart in 12; but in only three of these had a friction rub been heard. The three posterior infarcts on the posterior surface did not produce audible friction rubs.

Excluding the two cases complicated by uremia, the remaining ten with a generalized pericardial reaction fell into two groups. In the first were six cases with recent myocardial infarcts with which there was an acute fibrinous pericarditis; in the second, were four cases with old, healed infarcts and with a more or less firmly adherent pericardium. Three of the recent infarcts involved the anterior surface of the heart, and three the posterior surface. In two of the anterior and in all three of the posterior infarcts a friction rub had been heard during life. Thus the detection of a pericardial friction rub does not rule out the presence of an infarct on the posterior surface since this may cause a generalized pericardial reaction.

Short summaries of the ten cases of generalized pericardial involvement are appended.

SUMMARY

1. In 60 cases of coronary thrombosis with myocardial infarction examined at necropsy pericardial involvement was found in 48 (80 per cent).

2. In the 48 cases of pericardial involvement, the process was localized in 36 (75 per cent), and involved the entire pericardium in 10 (21 per cent). The pericarditis was generalized, but was possibly due to a coexistent uremia, in 2 (4 per cent).

3. A localized acute fibrinous pericarditis was present in 15 cases, but in only three of these had a friction rub been heard during life. A generalized acute fibrinous pericarditis was present in six cases. A friction rub had been heard in five of these, of which three showed the area of infarction to be limited to the posterior surface of the heart.

CASE SUMMARIES

CASE 1.—Unit History 49175. Path. No. 9116. White male, aged seventy-six years. Pain in left chest five days before death. Pericardial friction rub heard. Recent thrombus in left coronary artery. Infarct on posterior surface of left ventricle. "The visceral and parietal pericardium are firmly bound together by a fibrinous exudate which is 0.5 to 1 cm. in thickness in some places, thickest on the wall of the left ventricle."

CASE 2.—U. H. 50293. Path. No. 9130. Obese white female of sixty-four years. Pain twenty-three days before death. Friction rub heard. Circumflex branch of left coronary artery occluded. Infarct on posterior surface. "The epicardium is everywhere covered with a fibrinous exudate."

CASE 3.—U. H., 56243. Path. No. 9448. White male, aged fifty-two years. Attacks of precordial pain forty days and again three days before death. Friction rub heard. Recent thrombus in anterior descending branch of left coronary artery. Apical infarct. "The pericardium is everywhere bound to the heart with recent white fibrinous exudate."

CASE 4.—U. H. 58781. Path. No. 9456. White man of fifty-five years. Pain for a few days. Friction rub heard. Recent thrombus in anterior descending branch of left coronary artery. Apical infarct. "The anterior and lateral surfaces of the sac are everywhere bound to the heart by recent fibrinous exudate which is easily torn off."

CASE 5.—U. H. 244488. Path. No. 10397. White woman of fifty-four years. Pain for three days before death. Friction rub heard. Recent thrombus in right coronary artery. Infarct on posterior surface. "The entire surface of the heart, particularly the ventricles and the posterior portions, are covered with loosely adherent fibrin strands."

CASE 6.—U. H. 420724. Path. No. 11801. White male, aged fifty years. Attacks of pain ten months, five months, and one week before death. No friction rub. Old thrombus in anterior descending branch of left coronary artery; recent thrombus in right coronary artery. Infarcts on anterior surface and at apex. "Over the entire right auricle, a portion of the lateral and posterior walls of the right ventricle, and the posterior surface of the left ventricle there is a thin, shaggy, friable, light yellow exudate."

CASE 7.—U. H. 63053. Path. No. 9657. White male of seventy-four years. Pain followed by progressive congestive failure for eleven weeks before death. Anterior descending branch of left coronary artery occluded. Apical infarct. "The heart is covered by firmly adherent pericardium with complete obliteration of the sac."

CASE 8.—U. H. 63637. Path. No. 9663. White male, aged sixty-eight. No history of pain. Congestive failure for 2 days before death. Old occlusion of anterior descending branch of left coronary artery. Anterior surface infarct. "The pericardial cavity is completely obliterated by loose fibrous adhesions. . . . Where the pericardium had been separated, the epicardium is covered with fibrous tags."

CASE 9.—U. H. 63744. Path. No. 9673. White man of sixty years. No history of pain. Old thrombus in anterior descending branch of left coronary artery. Anterior surface infarct. "The pericardium is found thickened throughout and adherent to the heart."

CASE 10.—U. H. 56480. Path. No. 9828. White man of forty-two years. Angina pectoris for three years. Severe pain and friction rub a year before death. Old occlusion of anterior descending branch of left coronary artery. Anterior surface infarct. "The parietal pericardium is everywhere bound to the heart by dense adhesions."

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Special Article

STANDARDIZATION OF PRECORDIAL LEADS

Supplementary Report

THE American Heart Association and the Cardiac Society of Great Britain and Ireland have recently published[1] joint recommendations bearing upon the standardization of a single precordial lead for routine use. Many workers employ multiple precordial leads and the use of such leads is rapidly increasing. The Committee on Precordial Leads of the American Heart Association feel, therefore, that it is desirable to make recommendations with reference to leads of this type. They wish also to make public the considerations which led to the recommendations adopted.

MULTIPLE PRECORDIAL LEADS

When leads from two or more precordial points are employed, it is suggested that the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5000 or more ohms to electrodes on the right arm, left arm, and left leg. It is suggested further that in the first case the letters CF* followed by a subscript and in the second case the letter V followed by a subscript be employed to designate such leads.

The position of the precordial electrode shall be indicated by the subscript used according to the following plan: Subscript 1 shall be used for the right margin of the sternum; 2, for the left margin of the sternum; 3, for a line midway between the left margin of the sternum and the left midclavicular line; 4, for the left midclavicular line; 5, for the left anterior axillary line; and 6, for the left midaxillary line. When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the 4th intercostal space and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the 4th intercostal space to the outer border of the apex beat (or to a point at the junction of the midclavicular line and

*Those who prefer to place the distant electrode on the right arm may indicate its position by using the letters CR followed by a subscript. When this electrode is placed on the left arm, the letters CL followed by a subscript may be used. The letters R, L, and F are used as abbreviations for right arm, left arm, and foot (left leg), respectively. The letter C is an abbreviation for chest; T, for central terminal, and V, for voltage. The last (V) is used only in connection with unipolar leads in which the central terminal is the indifferent point.

the 5th intercostal space) and continued around the left side of the chest at the level of the apex beat or of the junction mentioned.†

EXPLANATORY REMARKS

Size of the Precordial Electrode.—There are at present no data upon which an accurate estimate of the most desirable size for the precordial electrode can be based. Theoretical considerations suggested that until such data become available it is desirable to employ a precordial electrode no larger than is required to avoid certain technical difficulties that may arise when a very small electrode is used. The technical difficulties in question depend upon polarization of the small electrode and high skin resistance when a string galvanometer is employed, and involve drifting of the baseline and interference due to extrinsic alternating current when the amplifier type of electrocardiograph is used. A circular electrode 3 cm. in diameter has been found satisfactory.

Single Precordial Leads.—The evidence at present available indicates that when a single precordial lead is used, the best place for the precordial electrode is at the outer border of the cardiac apex. An apical lead appears to give reliable evidence of infarction of the anterior wall of the heart and of abnormalities of the processes upon which the T-wave depends more often than any other single lead from the precordium. The normal variations of the precordial electrocardiogram in apical leads have been more thoroughly investigated than the normal variations of the precordial electrocardiogram obtained by leading from other points. The use of an apical lead has been objected to on the ground that it may be difficult for technical assistants to locate the cardiac apex. This objection applies more or less to all precordial leads. It is, perhaps, less valid in the case of sternal leads than others, but a single sternal lead is not satisfactory for the detection of infarction of the anterior or left lateral wall of the left ventricle.

Because the position of the second electrode is not always a matter of complete indifference, it was decided that it would be best to regard as permissible any of the positions of this electrode which have been specified and to devise a method of designating the one used. It was the general opinion that the committee should recommend one of the locations mentioned as the standard for routine use, but there was an almost even division of opinion as to whether the preference should be given to the right arm, for the sake of convenience in making the

†It will be noted that lead CF_4 and Lead IV F (or lead CR_4 and Lead IV R) may sometimes be identical. In the case of the latter (Lead IV F or Lead IV R), however, the precordial electrode is placed at the outer border of the cardiac apex regardless of the position of the apex with reference to the bony landmarks of the chest, whereas in the case of the former (lead CF_4 or lead CR_4) this electrode is placed in the midclavicular line even when the cardiac apex is far to the left of this position.

galvanometer connections, or to the left leg, which has been much more widely used.*

Multiple Precordial Leads.—In certain cases of infarction of the anterior wall of the heart, multiple precordial leads are required to establish the diagnosis. Such leads sometimes disclose abnormalities of the T-deflection which would otherwise escape detection. In the differentiation of right from left bundle-branch block, and in the differentiation of right from left ventricular enlargement, multiple precordial leads are indispensable. The series of leads particularly emphasized, although not necessarily the best that may be devised, has nevertheless been shown to be of great value and has received sufficient study to establish reasonably adequate normal standards, and to establish the configuration of the changes in the ventricular complex which occur in the different leads of the series as a result of the more common cardiac abnormalities.

In the majority of cases there is no essential difference between the curves obtained when the precordial electrode is paired with an electrode on the left leg and those obtained when it is paired with a central terminal. Essential differences become increasingly common as the distance of the precordial electrode from the ventricular surface is increased.

Method of Making the Galvanometer Connections.—In taking precordial leads the majority of workers in America have hitherto made the galvanometer connections in such a way that relative negativity of the precordial electrode was represented in the finished curve by an upward deflection. Other workers here and abroad have made the galvanometer connections in the opposite way so that relative positivity of the precordial electrode was represented by an upward deflection. It was thought imperative that one or the other method be declared standard. After a great deal of discussion it was decided that the temporary inconvenience to the large number who have become accustomed to

*There is some evidence suggesting that a comparison of Lead IV B and Lead IV F may be useful in the diagnosis of acute pericarditis and of myocardial infarction involving both the anterior and the posterior walls of the left ventricle. Lead IV T seems to be as satisfactory as any of the other apical leads. Compared with the leads in which the apical electrode is paired with a single electrode in the back or on one of the extremities, it is much more nearly unipolar; i.e., it records the potential variations of the precordial electrode without distortion (or with minimal distortion) due to potential variations of the distant electrode. Whether this will prove to be an important advantage from a practical standpoint is as yet uncertain. This lead has the disadvantage that it requires special equipment and is less convenient to use than Lead IV F or Lead IV R. Lead IV L is the most convenient of all because, after Lead III has been taken, a single operation (the transfer of the left leg wire to the apical electrode) is required to obtain it. It has, however, been so little used that it cannot be recommended without reserve at this time. The relative merits of these different leads are in need of thorough investigation. The following relations between them may be pointed out.

$$\text{Lead IV R} = \text{Lead IV F} + \text{Lead II}$$
$$\text{Lead IV L} = \text{Lead IV F} + \text{Lead III}$$
$$\text{Lead IV T} = \text{Lead IV F} + 1/3\ (\text{Lead II} + \text{Lead III})$$

These equations are analogous to Einthoven's equation, which states that Lead II = Lead I + Lead III.

the first method would be more than overbalanced by the advantages offered by the second.*

The advantages of making the galvanometer connections in such a way that relative positivity of the precordial electrode is represented in the finished curve by an upward deflection and relative negativity of this electrode by a downward deflection are as follows:

1. This method makes it possible to assign the letters Q, R, and S to the individual deflections of the QRS group in exactly the same manner as in the case of the standard limb leads, without violating the general principle that, as far as possible, deflections which have the same origin or the same significance should invariably bear the same name. In particular, it makes it possible always to assign the same letter (R) to the onset of the intrinsic deflection, which signals the arrival of the impulse at the epicardial surface of the portion of the heart subjacent to the precordial electrode, without departing from the customary method of labelling the QRS deflections.

2. In cases of infarction of the anterior wall of the heart this method yields ventricular complexes characterized by abnormally large initial downward deflections (Q-waves) and sharply inverted T-waves of the "cove plane" or "coronary type." These complexes are practically identical with those which have long been considered characteristic of myocardial infarction in the case of the standard leads, and they may be described in the same terms.

3. The P-deflections and T-deflections are normally upright. There are great advantages, particularly from the standpoint of one who is teaching electrocardiography or of one who is beginning the study of this subject, in a system which makes upright T-waves invariably normal, whatever the lead.

4. The use of the terms plus and minus and of the symbols + and − is greatly simplified. In the case of precordial leads one electrode, the precordial electrode, is much more important than the other. In the discussion of the principles upon which the interpretation of the precordial electrocardiogram rests, it is necessary to refer frequently to the potential of the precordial electrode and in connection therewith to employ the terms and symbols mentioned. Since we are accustomed to speak of downward deflections as negative and to prefix measurements of such deflections with the minus sign, much confusion and misunderstanding will be avoided if the deflection of the trace is upward when the potential of the precordial electrode is positive and downward when the potential of this electrode is negative.

*To make the galvanometer connections in such a way that positivity of the precordial electrode will produce an upward deflection in the finished record, it is necessary to connect the left-hand wire to this electrode if the lead switch is on Lead I and to connect the left-leg wire to this electrode if the lead switch is on Lead II or Lead III. To take Lead IV F, connect the left-leg wire to the precordial electrode and the left-arm wire to the left-leg electrode and place the lead switch on Lead III. To take Lead IV R, connect the left-leg wire to the precordial electrode and the right-arm wire to the right-arm electrode and place the lead switch on Lead II.

Nomenclature.—For the convenience of those who wish to make statistical studies of the QRS group, to measure and tabulate the QRS deflections, or to classify or characterize QRS deflections of different types, it is imperative that the individual deflections of the QRS group be designated by distinct symbols, even though the naming of these deflections may involve the application of rules that are more or less arbitrary.

The adoption in the case of precordial leads of symbols different from those employed in the case of the standard leads might have some advantages. It would, however, have at the same time tremendous disadvantages. It would add an entirely new terminology to clinical electrocardiography which is already regarded by many as an abstruse and incomprehensible subject, and would greatly increase the number of technical terms which beginners in this field would have to learn. It would invite other attempts to improve upon electrocardiographic terminology, and would stand little chance of prompt and universal acceptance. The adoption of new symbols for the initial ventricular deflections would also greatly complicate the use of such terms as the P-R interval, the QRS interval, the RS-T segment, and RS-T displacement which could not then logically be used with reference to precordial leads. For these reasons it was decided that the deflections of precordial leads should be designated by the same letters as those of standard limb leads.

Comments.—In making the recommendations adopted it has been our purpose to simplify the use of precordial leads for those who desire to employ them in everyday clinical work, and to reduce the confusion that exists at present because of a lack of uniformity and precision in current technique and nomenclature. Our discussions have made us acutely aware of many gaps in our knowledge of the precordial electrocardiogram which must be filled in by future investigation. We feel that it would be unfortunate if our attempt to standardize precordial leads should discourage the investigation of leads of any kind whatsoever.

Signed

Arlie R. Barnes
Harold E. B. Pardee
Paul D. White
Frank N. Wilson
Charles C. Wolferth

Committee of the American Heart Association for the Standardization of Precordial Leads

REFERENCE

1. Standardization of Precordial Leads: Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, AM. HEART J. 15: 107, 1938.

Department of Clinical Reports

CORONARY THROMBOSIS IN A CASE OF CONGENITAL DEXTROCARDIA WITH SITUS INVERSUS*

J. HAMILTON CRAWFORD, M.D., AND CHARLES FORD WARREN, M.D.
BROOKLYN, N. Y.

COMPLETE transposition of the viscera, although uncommon, is of no clinical importance as the organs function in a normal manner. Individuals with this abnormality are liable to be affected by the same diseases as afflict those in whom the organs are in a normal position. The following case of situs inversus is presented because the patient suffered from acute coronary thrombosis and, as far as can be determined, no previous case has been reported of this nature.

CASE REPORT

E. O., a male, fifty-eight years of age, stated that on June 15, 1935 while plastering a wall, he felt his back snap. He developed a severe pain in the lumbar region and slight pain in the chest. He was treated for the back injury which slowly improved but about the middle of July while walking in the street he was seized with severe constricting pain just to the right of the sternum. The pain lasted for about an hour and there was a feeling of numbness in the right arm. Since that time he has had attacks of pain in this situation on exertion or excitement but some have occurred without any apparent cause. They were usually preceded by numbness of the right arm. An attack usually lasted from one-half to one hour but the most severe attack, which took place in September, lasted two hours. There has been no radiation to the left arm or to the neck. He had had slight dyspnea on exertion from time to time but otherwise the history was negative. Patient stated that he had always been right handed. He was admitted to Kings County Hospital on Nov. 20, 1935 and was discharged much improved on Jan. 17, 1936.

Physical examinations revealed a slightly overweight man with some cyanosis of the mucous membranes. The radial and retinal arteries showed sclerotic changes consistent with his age. The pulse was regular at a rate of 68 beats per minute and the blood pressure was 154/84. On examination of the heart the condition of dextrocardia was found, with the apex just outside the right midclavicular line. There was a localized systolic murmur at the apex but no other murmurs were audible. The sounds at the base were faint. There were scattered dry râles on both sides of the chest at the base. The liver was situated on the left side. No edema was present. Routine laboratory studies, including urine, blood, blood chemistry, and Wassermann test, were negative.

Electrocardiograms.—Lead I showed the characteristic features of congenital dextrocardia with inversion of all the complexes; Lead II an inverted P-wave, a deep Q and definite coving of the RS-T segment, with a deep negative T-wave; Lead III a small Q-wave, slight slurring of R, some coving of the RS-T segment followed by a negative T; Lead IV (right arm electrode on apex and left arm electrode just below the angle of right scapula) appeared essentially normal (Fig. 1). The diagnosis was that of previous coronary thrombosis in a case of congenital dextrocardia.

*From the Department of Medicine, Long Island College of Medicine, and the Department of Cardiology, Kings County Hospital.

In order to clarify the situation and make the curves comparable to those usually studied for coronary thrombosis, tracings were made in which the left arm electrode was placed on the right arm, the right arm electrode on the left arm, and the left leg electrode on the right leg (Fig. 2). Lead I was normal except for a slight slurring of R; Lead II showed a small Q-wave and some coving of the RS-T segment with a negative T-wave; Lead III had a diphasic P-wave, a deep Q-wave, marked coving of the RS-T segment and a deep negative T-wave. Were such curves obtained in an individual with the heart in the normal position the diagnosis of a previous coronary thrombosis of the T_2 type with the infarct on the posterior surface of the left ventricle would appear to be justified.

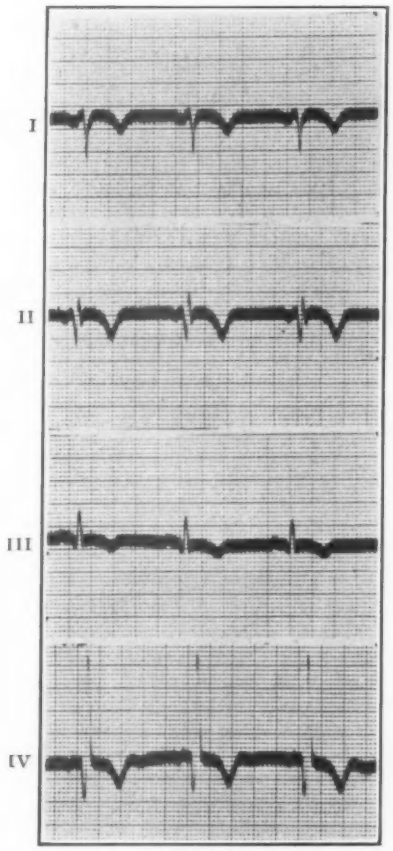

Fig. 1.

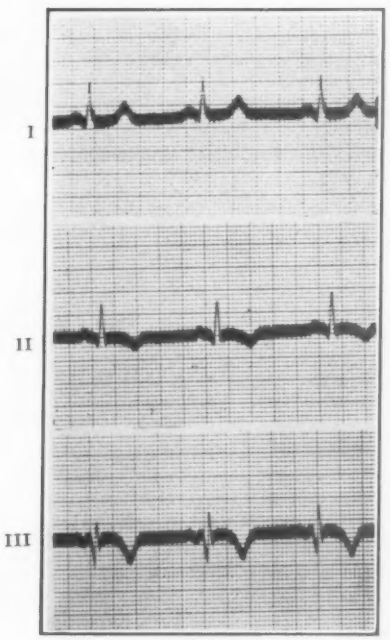

Fig. 2.

Fig. 1.—Standard leads and Lead IV (right-arm electrode-apex, left-arm electrode below angle of right scapula).

Fig. 2.—Left-arm electrode on right arm, right-arm electrode on left arm, and left-leg electrode on right leg.

Roentgenograms.—A six-foot teleroentgenogram of the chest showed dextrocardia with very slight cardiac enlargement (Fig. 3). In order to demonstrate the complete transposition of the abdominal viscera the stomach was filled with barium and a barium enema given (Fig. 4).

SUMMARY

A case of congenital dextrocardia with situs inversus is presented in which there is good evidence that a previous coronary thrombosis had taken place. The most interesting feature is the distribution of the

pain during the attacks of angina pectoris. Before and after the attacks a feeling of numbness appeared in the right arm. The pain was localized strictly to the right side of the chest and there was no radiation to the left arm or neck. When the organs are situated in their normal position the pain is usually localized to the left side of the chest

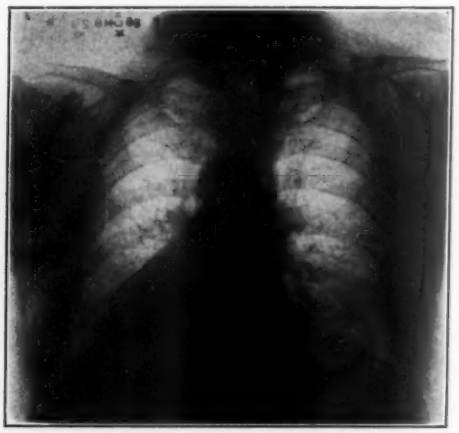

Fig. 3.—Teleroentgenogram of chest at six-foot target distance.

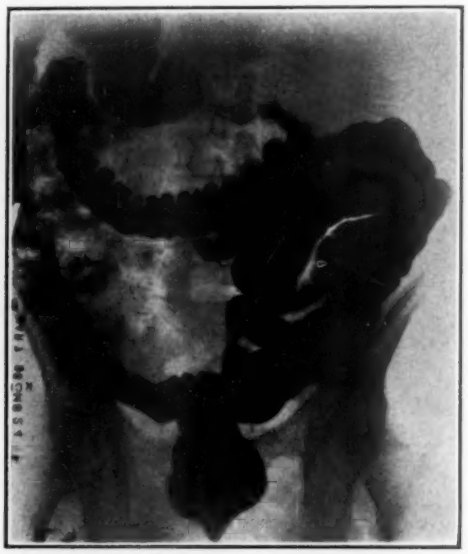

Fig. 4.—X-ray film showing complete transposition of abdominal viscera.

with radiation to the left arm although the pain may sometimes extend to the right chest with radiation to both arms or to the right arm alone. Anatomical evidence shows that the sensory nerve supply from the heart is bilateral and that impulses pass to both sides of the spinal cord. It seems probable however that when the heart is normally situated the main pain pathways run to the left side of the cord while the present case suggests that in dextrocardia they enter on the right side.

SUDDEN DEATH IN AORTIC STENOSIS

Explanation on a Mechanical Basis*

J. Arnold deVeer, M.D.
Brooklyn, N. Y.

IN 1935 Marvin and Sullivan[1] called attention to the fact that patients with stenosed aortic valves are liable to die unexpectedly and suddenly. It had not, until then, been widely known that such a hazard exists in cases of this type, although occasional generalizations on the subject were found in the literature. These investigators reported a group of eleven cases of aortic stenosis in nine of which death had been very sudden when the patients appeared to be in their usual health. Four of the nine did not have heart failure at the time. In four of the cases autopsies were performed, but in only one instance was an apparent cause of the sudden death discovered, namely, a complete closure of the narrowed aortic aperture by a thrombus which was thought to have formed during life. The authors found record of a similar instance of thrombotic obstruction of a stenosed aortic valve ostium in a paper by Lutembacher.[2] In this case the stenosis had been attributed to rheumatic valvulitis. In all other cases that Marvin and Sullivan found recorded there had been no anatomical findings to explain the sudden death.

These authors reviewed the various possible causes of sudden death, rejecting as improbable such processes as embolic closure of a large artery (coronary or cerebral), or sudden occlusion of the small aortic orifice by a blood clot (at most a rare event if the two cases referred to be considered authentic instances of ante-mortem occlusion). The mechanical narrowing of the aortic orifice is not, of itself, to be regarded as an adequate explanation. They suggest that the size of the heart may be of some importance, since in their cases enlargement of the heart was greater in those patients who died suddenly than in the others. The authors discuss the occurrence of syncopal attacks in five of their patients, three of whom died very suddenly, and advance the idea that both the syncope and sudden death may be due to the cardio-inhibitory action of the carotid sinus reflex.

No subsequent discussion of the subject has appeared in the literature.

The following mechanical explanation of sudden death was arrived at through examination of the heart in a single case of aortic stenosis. The writer has at hand no other material on which to test out his hypothesis, and it is with the hope that others may be in a position to do so, that this report is presented.

*From the Department of Pathology of The Brooklyn Hospital.

CASE REPORT

R. W., a fifty-nine-year-old white male, was admitted to the service of Dr. William H. Lohman at the Brooklyn Hospital on Oct. 6, 1936. Throughout the previous year he had noted dyspnea on exertion and, for the previous two weeks, paroxysmal dyspnea. Physical examination showed pulmonary congestion, the heart enlarged to the left, and the heart sounds of poor quality. There was a systolic thrill and a coarse systolic murmur at the aortic area. The aortic second sound was diminished. The pulse was small and of the plateau type. An electrocardiogram was interpreted as indicating left heart strain. Examination by roentgen ray showed

Fig. 1. Fig. 2.

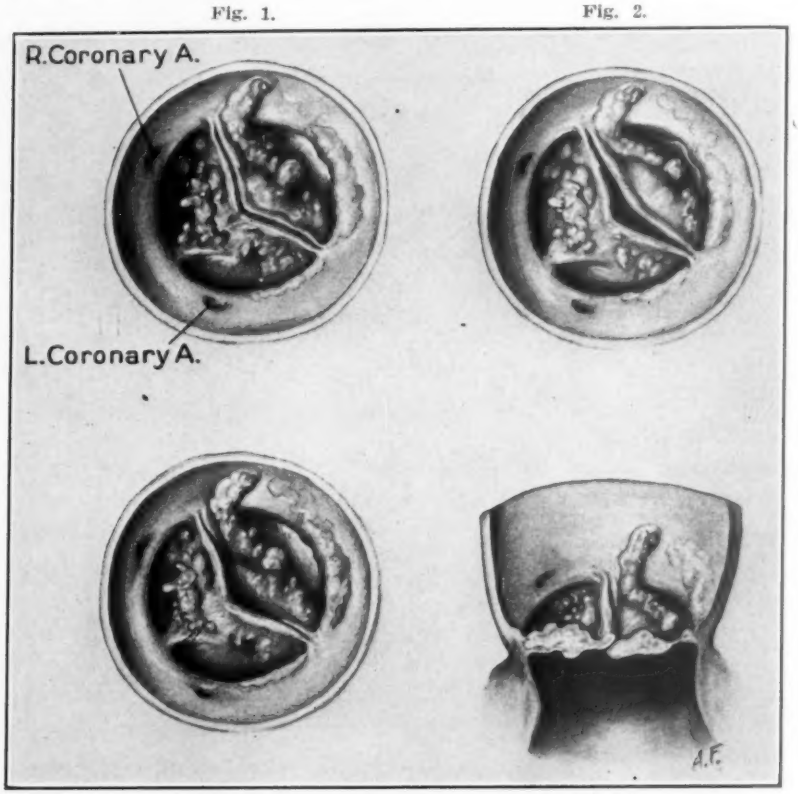

Fig. 3. Fig. 4.

Fig. 1.—The aortic valve in the position of closure, showing perfect apposition of the edges of the cusps. The fused cusps are each somewhat smaller than the free cusp, simulating a congenital bicuspid valve. Nodular calcareous deposits are seen on the valve and extending onto the aortic wall.

Fig. 2.—The valve in the position assumed during systole. The free cusp is slightly elevated producing a slit-like orifice.

Fig. 3.—The valve in the "locked" position. Slight pressure on the aortic surface of the free cusp served to force it below the margin of the fused cusps. It assumed this position with a little "snap" or click as of a closing door latch.

Fig. 4.—A cross-section through the commissure of the fused cusps and the center of the free cusp. Note the horizontal position of the cusps.

only enlargement of the heart. Renal function was within normal limits. The blood pressure ranged from 170/130 to 175/140. The condition was diagnosed as aortic stenosis on an arteriosclerotic basis. After a stay of four weeks the patient was discharged from the hospital greatly improved and was instructed to report to the clinic.

On Jan. 7, 1937 the patient came to the hospital as a visitor. He spoke animatedly with an interne, who found his pulse to be 90 and remarked on his apparent good health. Ten minutes later, while still at the hospital, the patient collapsed. Within a few moments a physician found him pulseless, with shallow irregular respirations which then ceased. Efforts at resuscitation were of no avail.

At autopsy generalized arteriosclerosis and a moderate degree of chronic passive congestion were found. Other significant pathological changes were confined to the heart, which weighed 650 gm. The pericardium was smooth, thin, and without adhesions. There was enlargement of the entire heart but hypertrophy of the left ventricle was particularly marked. The left ventricular wall measured from 2 to 3 cm. in thickness. There was a relatively great hypertrophy of the musculature of the right ventricle and of the atria, and all of the chambers were moderately dilated. The coronary arteries showed a moderate degree of sclerosis but were not markedly narrowed and contained no thrombi. The tricuspid and pulmonary valves were normal. The mitral valve ring was calcified and there were a few atheromatous plaques on the anterior cusp. There were no adhesions between the cusps and the valve was otherwise normal. The aortic valve was the seat of advanced sclerosis of the Moenckeberg type, with a high grade stenosis. This valve will be described in some detail, since the mechanism suggested as responsible for the sudden death of the patient is based entirely on the condition of the stenotic valve.

All of the aortic cusps were thickened and heavily calcified, and projected rigidly into the lumen of the vessel. The right anterior and left posterior cusps were completely fused. The remaining cusp, the right posterior, was not adherent. The two fused cusps were entirely immobile and formed a kind of shelf occluding about two-thirds of the ostium. The third cusp was also entirely rigid, could be moved but very little and only by virtue of slight flexibility of the wall of the vessel at the base of the cusp. In diastole this free cusp closed the ostium perfectly by resting against the edges of the "shelf" formed by the fused cusps (Fig. 1). In systole it could be lifted slightly to produce an angular, slit-like opening (Fig. 2). It required very little pressure at autopsy to push the free cusp downward under the edge of the shelf, where it remained securely locked (Figs. 3 and 4). More pressure was required to release it than to lock it.

The position of the free cusp at autopsy was not observed until there had been considerable dissection and handling of the specimen, in fact the possibility that such a locking mechanism might have operated as the cause of the sudden death of the patient was not at first considered. It cannot, then, be stated that the valve was found in the locked position, but only that both before and after fixation of the tissue in Klotz solution this mechanism could be demonstrated very convincingly.

The cusps of the valve projected inward from the aortic ring almost at right angles to the wall of the aorta, and the free cusp, therefore, received very little support from the fused cusps during diastole. It seems possible that an unusually forceful diastolic recoil thrust might have served to force the free cusp below the margin of the fused cusps during life, just as it could be pushed down with the examining finger at autopsy.

The writer does not contend that all cases of sudden death in aortic stenosis can be explained by such a mechanism. Obviously it could

operate only with valves showing a type of stenosis similar to the one herein described, the so-called acquired bicuspid valve, and not in cases of complete fusion of the cusps. Satisfactory demonstration of such a mechanism would require careful inspection of the valve prior to the introduction of instruments or examining fingers which would serve to dislodge the locked cusp.

REFERENCES

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2. Lutembacher, R.: La Mort subite chez les cardiaques, Presse méd. 29: 203, 1921. Cited by Marvin and Sullivan.

Department of Reviews and Abstracts

Selected Abstracts

Goormaghtigh, N.: The Structure of the Auricles of the Heart. Arch. f. Kreislaufforsch. **1**: 377, 1937.

The auricles of the heart show characteristically many blood filled balloon-like protrusions into the wall. These protrusions can be cut off easily from the heart cavity by the muscle trabeculae which surround their slitlike openings.

KATZ.

Kiese, M., Gummel, H., and Garan, R. S.: The Absorption of G-Strophanthin by the Liver in the Heart-Lung-Liver Preparation. Arch. f. exper. Path. u. Pharmakol. **184**: 197, 1937.

This was determined by comparing the lethal dose of G-strophanthin in the heart-lung and heart-lung-liver preparation of the dog. When the blood flow of the heart and the liver was about the same per kilo, it was found that the liver took up less G-strophanthin per gram than the heart. It could be shown that liver binding of G-strophanthin was a function of the concentration of the drug in the perfusing blood. Livers damaged by ischemia took up less of the drug than undamaged livers.

KATZ.

Wolf, H. J., Mohr, M., and Kröger, E.: Residual Blood Flow of the Kidney After Ligation of the Main Artery. Ztschr. f. d. ges. exper. Med. **100**: 485, 1937.

The authors believe from previous work that the production of tyramine has to do with the hypertension which develops after complete ligation of one renal artery. In the present study, the left renal artery was ligated in six dogs. In five, the blood flow from left and right renal veins was measured five to seven days later; in the sixth, one-half hour later. The blood flow was found to be from one-tenth to one-quarter that on the normal side. Secretion of urine did not occur in the kidney deprived of its blood supply. The vessels of the capsule were markedly dilated. This residual circulation is considered to be the source for the transportation of tyramine into the general circulation.

STEELE.

Biehler, W.: Veritol (H 75), a New Circulatory Drug With Peripheral Action. Ztschr. f. d. ges. exper. Med. **101**: 62, 1937.

β-p-oxyphenyl-isopropylmethylamin marketed under the name of "veritol" was studied by Biehler in cats, rabbits, guinea pigs, and mice. He finds that its action upon arterial pressure lies between that of adrenalin and ephedrin and that its pressor effect is somewhat greater than the related compounds tryamine and hordenine. Intravenously it is effective in approximately $\frac{1}{2000}$ of the lethal dose. It is, furthermore, effective by mouth in rabbits in doses approximately $\frac{1}{80}$ of the lethal dose. Like adrenalin, reversal of the pressor effect occurs after ergotamine and yohimbin. The drug's point of attack, he believes, is both cardiac and peripheral.

STEELE.

Heinlein, H.: Changes in Organs Due to the Substances Native to the Body Which Act Upon the Circulation: I. Histamin. Ztschr. f. d. ges. exper. Med. 100: 661, 1937.

The author fed histamin to cats over periods varying from one to three months in quantities sufficient to induce vomiting, as he had previously done with rabbits. He finds histologic lesions chiefly in heart and lungs but to a lesser extent also in liver, spleen, and kidneys. The lesions appear to be dependent upon swelling and breaking down of the intima of the arterioles, fibrin formation beneath, and focal swelling and necrosis of the media. Focal necrosis of the heart and liver was found with leucocytic infiltration and in the kidney marked stasis of the capillary tufts of the glomeruli, protein and occasional red cells in the capsular space with swelling and dissolution of the capsular epithelium. He points out the similarity of these lesions to those obtained in animals made allergic to foreign proteins.

STEELE.

Heymans, C., and Bayless, F.: Concerning the Action of β-p-oxyphenyl-isoprophyl-methylamine. Arch. internat. de pharmacodyn. et de thérap. 56: 319, 1937.

The authors confirm the work of Biehler and of Rein that β-p-oxyphenyl-isopropylmethylamine, a synthetic compound related to tyramine and hordenine, is a mild pressor substance. By means of crossed circulation experiments in donor and recipient dogs they show that its action is due to peripheral vasoconstriction, rather weak in the general periphery, but well marked in the splanchnic region. In the intact animal the pressor effect is very small, as Rein found, because vagal slowing offsets its effect, but in atropinized or vagotomized animals a considerable rise in pressure may occur.

STEELE.

Heymans, C., and Bayless, F.: Influence of Anesthesia by Morphine-Pernoctone and by Chloralosane Upon the Arterial Pressure and Upon the Vasomotor Reflexes of the Proprioceptive Regulation of Arterial Pressure. Arch. Internat. de pharmacodyn. et de thérap. 56: 419, 1937.

The effect of closure of both carotid arteries upon arterial pressure carried out in dogs under local anesthesia is compared with the effect of closure of the arteries carried out later in the experiments under (1) morphine-pernoctone and (2) chloralosane anesthesia. The results show that the former tends to depress markedly arterial pressure as well as the means of regulating it while the latter does not. He concludes that Rein's statements that morphine-pernoctone does not influence any of the known vasomotor reactions is unjustified and that chloralosane is a very suitable anesthetic for studies of the physiology of the circulation.

STEELE.

Katz, Louis N., and Feil, Harold S.: Clinical Observations on the Dynamics of Ventricular Systole. IV. Pulsus Alternans. Am. J. M. Sc. 194: 601, 1937.

The dynamics of systole in five clinical cases of pulsus alternans were studied by optical registration methods. The following conclusions were reached:

The alternation in the size of the pulse is accompanied by concordant alternations in the heart sounds, the gradient of the pulse and the duration of ejection, and by a discordant alternation in the duration of the isometric period. The duration of total systole showed no alternation.

No alternations were found in the electrocardiograms in this series, although conduction disturbances were present in four of the cases.

The duration of diastole did not vary consistently and was so small as to be without significance in explaining the alternation of the pulse volume.

In the case with complete heart-block the pulsus alternans is attributed to contribution of auricular stimuli in alternate diastoles.

The evidence presented in this report, when correlated with previous studies of the dynamics of systole, supports the view that changes in initial volume and tension such as follow extrasystoles and sudden changes in rhythm and in respiration (so often present in alternation) can help to initiate the phenomenon of pulsus alternans. Once established, alternate variations in systolic residue occur which alternately increase and decrease the initial tension and volume and so help to perpetuate the phenomenon. It is not denied that changes in the refractory phase are important in initiating and perpetuating pulsus alternans, but it is emphasized that the changes in initial tension and volume are likewise important.

AUTHOR.

Steinberg, Israel, Clark, Eugene, and de la Chapelle, Clarence E.: Suppurative Pleuritis Complicating Pulmonary Infarction in Congestive Heart Failure. Am. J. M. Sc. **194**: 610, 1937.

In the foregoing report are presented the clinical and necropsy findings in four patients with congestive heart failure, in whom suppurative pleuritis complicated pulmonary infarction. The evidence discussed indicates that bland pulmonary infarcts may spontaneously undergo secondary infection which leads to empyema by penetration of the microorganisms to the pleura.

AUTHOR.

Wilkins, Robert W., Weiss, Soma, and Haynes, Florence W.: The Effect of Epinephrin in Circulatory Collapse Induced by Sodium Nitrite. J. Clin. Investigation **17**: 41, 1938.

The effect of epinephrine has been studied in vasomotor collapse induced by sodium nitrite in subjects in the upright position.

Both in the horizontal and in the upright positions, epinephrine in subcutaneous doses of 1 mg. caused arteriolar constriction in and decreased blood flow through the hand. The venous tone was increased, as was the arterial pulse pressure and the heart rate; the venous pressure was usually slightly elevated.

Epinephrine did not prevent the vasomotor collapse and syncope produced by sodium nitrite, mainly because the arteriolar constriction and the tissue anoxia were enhanced and because the decreased venous tone produced by nitrite was not adequately compensated for.

The experiments indicate that the level of the arterial pressure is not a reliable index of the clinical manifestations of vasomotor collapse or of the degree of tissue anoxia.

The study presented throws light on the treatment of different types of vasomotor collapse. The fact that epinephrine is ineffective in nitrite collapse does not rule out its efficacy in other types of collapse.

AUTHOR.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathologic States—I and II. Ztschr. f. d. ges. exper. Med. **99**: 158 and 371, 1936.

Benzidine coloring of erythrocytes was used to study the flow in the smallest vessels in the heart muscle during systole and diastole. A brisk circulation was found to occur during systole. The number of functioning anastomoses decreased.

Toward the end of systole there is a hindrance to venous flow. In diastole there is dilatation of the smallest vessels and the appearance of a rich anastomotic network. The picture is the same on the outer and inner layers of the heart. No evidence exists of an extravascular compression of the capillaries during systole. The systolic flow is maintained by elevation of the coronary arterial pressure and the arteriole widening in this phase.

In cardiac hypertrophy there is a noticeable increase in the number of active capillaries and vicarious anastomoses, while in dilatation there is a diminution of the normal blood flow and an increase in the anastomotic circulation.

KATZ.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathological States—III. Ztschr. f. d. ges. exper. Med. **99**: 387, 1936.

In diphtheritic myocarditis of the guinea pig heart, one finds first a myocardial active hyperemia and then an ischemia when fatty degeneration of the heart occurs. Around these ischemic areas new capillaries appear which indicate the onset of the reparative stage.

KATZ.

Vannotti, A.: The Capillaries and Nourishment of the Heart and Large Vessels Under Normal and Pathological States—IV. Ztschr. f. d. ges. exper. Med. **99**: 557, 1936.

Diffusion of vital dyes occurs normally through the endocardium of the aorta and through the capillaries of its adventitia. In hypertension there is a decrease in the latter diffusion and an increase in the transintimal diffusion. Histologically, one can also demonstrate medial necrosis and calcification. Apparently only in the valves and auricles is endocardial diffusion adequate to nourish underlying structures, but this is not the case in the aorta.

KATZ.

David, F., and Siedek, H.: Bloodless Method of Measuring Pressure in the Pulmonary Artery. Ztschr. f. d. ges. exper. Med. **100**: 54, 1936.

With a bronchoscope, one can see pulsations in the right bronchus 1 cm. below the bifurcation of the trachea. A small rubber balloon is adjusted to cover this region, and the pulsations recorded with varying pressures within the balloon. The oscillograms permit the determination of the pressure on Marey's principle. In twenty dogs this pressure was found to be 30 per cent of the systemic. In two experiments the author found a favorable comparison between the indirect and the direct measurements. In man the author found a similar relation between pulmonary and systemic pressure.

KATZ.

Blumgart, Herrman L., Hoff, Hebbel E., Landowne, Milton, and Schlesinger, Monroe J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes. Am. J. M. Sc. **194**: 493, 1937.

Since, according to current belief, angina pectoris and cardiac infarction are the result of myocardial ischemia, experiments were undertaken to learn whether temporary interruption of the blood supply to a portion of the heart would result in persistent electrocardiographic or anatomic changes.

Occlusion of the left anterior descending coronary artery or one of its branches for from five to forty minutes with subsequent release of traction was performed in twenty-four cats. Twenty-one animals were allowed to survive for from one to nine days after this procedure.

Electrocardiograms of the three conventional leads obtained before and at various intervals during and following occlusion revealed anoxemic changes persisting during the postoperative days in all animals in which occlusion was maintained for from fifteen to forty minutes, inclusive. Only three of six animals in which the period of occlusion was ten minutes or less showed changes on the postoperative days; in one these changes persisted until sacrifice of the animal eight days postoperatively. The electrocardiographic changes were characteristic of the anterior infarction type.

Post-mortem examination failed to reveal gross or histologic evidences of cardiac infarction in any instance.

Cardiac irregularities consisting of ventricular extrasystoles and ventricular fibrillation were observed at times during occlusion but particularly on release of traction. Three of the five animals which developed ventricular fibrillation died immediately.

The clinical counterparts of these experimental observations are discussed.

AUTHOR.

Draper, George, Bruenn, Howard G., and Dupertuis, C. Wesley: Changes in the Electrocardiogram as Criteria of Individual Constitution Derived From Its Physiological Panel. Am. J. M. Sc. **194**: 514, 1937.

A precision method has been used to study a constitutional character in the physiologic panel.

There is a high degree of constancy over long periods of time in the individual electrocardiographic pattern demonstrated in one or both of (a) an unchanging pathologic state (Einthoven) and (b) the circumstance of a continually normal heart.

Significant differences between the electrocardiographic curve patterns for ulcer and gallbladder patients appear to exist within certain age groups.

These differences are also significantly distinct from the electrocardiograms of individuals with normal records selected from a general hospital population.

AUTHOR.

Lucke, H.: Cardiac Arrhythmias of Central Origin. Deutsches Arch. f. klin. Med. **180**: 40, 1937.

Two cases are reported, one of cerebral confusion (commotio cerebri) and the other of brain stem involvement, in which cardiac arrhythmias of vagal origin (since atropin tended to abolish them) occurred. In one case the arrhythmia was in the nature of extrasystoles and in the other there was sinus bradycardia and arrhythmia, multiple ectopic beats, and first and second degree A-V block.

KATZ.

Tochowicz, L.: The Clinical Value of the Dorsoventral Lead. Ztschr. f. Kreislaufforsch. **29**: 711, 1937.

In 280 cases with stenocardia, it was found that using four leads increased the electrocardiographic evidence from 50 per cent, obtainable with the limb leads alone, to 80 per cent when the fourth lead is added. This the author states is one of the reasons this lead is valuable.

KATZ.

Bloch, C.: Resemblance in the Appearance of Automatic and Extrasystolic Beats. Cardiologia **1**: 186, 1937.

Six cases are reported in which extrasystoles and automatic beats had the same electrocardiographic contour and the pauses between the automatic beats were multiples of the extrasystolic coupling. These rhythms occurred in cases with serious heart disease, or following digitalis, carotid sinus pressure or exercise. These two types of beats are from the same focus. The presence of "exit" block is important in this mechanism and relates it to parasystole.

KATZ.

Boyd, Linn J., and Werblow, S. Charles: Coronary Thrombosis Without Pain. Am. J. M. Sc. **194**: 814, 1937.

Additional evidence is submitted to support the idea that major coronary thrombosis may occur without pain. Pain was not present in one-third of 127 cases of coronary thrombosis observed by the writers during a twenty-five-month period although its occurrence was the subject of particular inquiry.

Seven cases of this type are reported briefly. The occurrence of three cases in females among 7 reports is suggestive of the increasing occurrence of coronary thrombosis in women. Although Metropolitan Hospital has a large negro clientele, only 1 colored patient is reported, and he was the son of a white father and half-white mother.

Most of the cases were known to be cardiac and had manifested more or less cardiac failure for periods varying from a few weeks to many years. Sudden inexplicable increased congestive failure in a known cardiac patient should arouse suspicion of coronary thrombosis; moreover in such cases pain is usually absent. There was 1 case of a pain equivalent in the form of "choking," several of severe vertigo, commonly associated with periods of unconsciousness, and 1 of a painless episode in the so-called "digestive" group.

The diagnosis of painless coronary thrombosis, as a rule, should not be difficult if the possibility is considered. Our mistakes have occurred mainly in elderly individuals with known arteriosclerotic heart disease and hypertension.

Painless coronary thrombosis probably occurs more frequently than is generally appreciated, and we may assume that mild cases are more common than the fatal examples reported in this paper.

As the histories of these patients are singularly free from pain, they may belong to Libman's hyposensitive group. It is suggested that greater attention should be paid to the nerve plexuses surrounding the coronary vessels in cases of painless coronary infarction.

AUTHOR.

Levy, Robert L., and Golden, Ross: Roentgen Therapy of Active Rheumatic Heart Disease. A Summary of Eleven Years' Experience. Am. J. M. Sc. **194**: 597, 1937.

Forty-eight patients with rheumatic heart disease have been treated by roentgen irradiation of the heart and have been observed during the past eleven and one-half years.

In a considerable number the evidence indicated that radiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease. Those receiving the larger number of treatments, as a general rule, fared best.

Irradiation relieved cardiac pain in patients who did not have aortic insufficiency.

No harmful effects were noted. Unpleasant radiation reactions appeared in about half the cases.

Cases with low grade activity and without signs of congestive heart failure appear to be most benefited.

The manner in which improvement is initiated is not known. It is believed to be due to an altered response of the cardiac tissues induced by the rays.

Roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

AUTHOR.

Dawson, W. S.: Cerebral Arteriosclerosis: A Review. Australia 2: 499, 1937.

While arteriosclerosis may be inferred with a fair degree of certainty when mental deterioration, with or without focal signs, occurs in the subject of general arteriosclerosis, in many more cases the existence of this pathologic change can be suspected only during life, and final proof depends upon the results of microscopic examination. Even so, the older the patient, the greater will be the probability, that simple neuronic decay is the major factor in the clinical condition, with the reservation that cerebral arteriosclerosis cannot be excluded until the brain has been examined microscopically.

AUTHOR.

Wollheim, E.: A New Depressor Substance and Its Relation to the Pathogenesis of Essential Hypertension. Schweiz. med. Wchnschr. 66: 1231, 1936.

A new thermostable depressor substance, not related to other depressor substances, was obtained from the human urine, horse's urine, and the posterior lobe of the pituitary gland of the cow. The author calls this substance depressan and finds that it is related to human essential hypertension, in that it is absent in the urine of hypertensive subjects. He concludes that hypertension is the result of a deficient production of this substance.

KATZ.

Wallis, O.: Action of Folliculin on the Blood Pressure. Zentralbl. f. Gynäk. 60: 2839, 1936.

In 12 cases of essential hypertension (8 females and 4 males), the follicular hormone had no depressor action.

KATZ.

Dozzi, Daniel L.: Cerebral Embolism as a Complication of Coronary Thrombosis. Am. J. M. Sc. 194: 824, 1937.

One thousand consecutive, unselected autopsies were analyzed for the incidence of cerebral embolism and cerebral thrombosis in patients known to have coronary thrombosis. The same series was then analyzed for the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage, cerebral thrombosis, and cerebral embolism.

Of the 1,000 patients, brains of 138 were examined at autopsy. Of these, 107 had either cerebral hemorrhage, cerebral thrombosis, or cerebral embolism. Of these 107 coronary thrombosis also occurred in 12 cases (11.2 per cent). The latter lesion was not diagnosed clinically in a single case and suspected in only 2.

While there were 41 cases of coronary thrombosis in the series of 1,000 autopsies, only 29 of these were clinically recognized and recorded. The remaining 12 were found as clinically unsuspected coronary thromboses in the autopsy records of the 107 cases that had a clinical diagnosis of either cerebral hemorrhage, cerebral

thrombosis, or cerebral embolism. None of the 29 cases clinically recognized was shown to be associated with a cerebral lesion. The association of 12 of the 41 cases of coronary thrombosis with a cerebral vascular lesion gives an incidence of 29 per cent, a higher figure than those found in the literature.

Though this series is too small to permit definite conclusions, this indication of a high incidence of unsuspected coronary thrombosis in cases of hemiplegia should serve as a stimulus for more extensive study and investigation.

As a result of the findings of this study, the following suggestions present themselves:

1. While it is generally felt that the heart is frequently the source of a cerebral embolus in persons under forty years, it would be wise to suspect the heart in all cases of cerebral embolism, irrespective of the patient's age.

2. When suspecting the possibility of coronary thrombosis as the etiologic factor in a case of hemiplegia, we must bear in mind the atypical forms of coronary thrombosis and must not lose sight of the fact that in cases with congestive heart failure the coronary thrombosis might be masked by dyspnea.

All cases of hemiplegia should have a careful search made for any clue leading toward old or recent coronary thrombosis in addition to routine electrocardiographic tracings.

4. In order to establish the true incidence of cerebral embolism or cerebral thrombosis as a sequel of coronary thrombosis, we must examine the heart at autopsy in all cases that clinically have a cerebral lesion. Also we must examine the brain in all cases with coronary thrombosis with any neurologic manifestations.

AUTHOR.

Prettin, F.: Thrombosis and Fatal Lung Embolism. Virchows Arch. f. path. Anat. **297:** 535, 1936.

A study based on necropsy material shows that postoperative fatal lung embolism occurs especially in abdominal operations, most often from the third to the eighth postoperative day. The primary thrombi were located most often in the inferior vena cava, iliac veins, femoral veins or prostatic or uterine plexus. Deaths were more frequent over the age of forty and increased with age. In 135 out of 229 cases, marked arteriosclerosis of the heart and blood vessels was found. Women with this condition were on the average 11 kilos over the average normal weight and men on the average 4.2 kilos overweight. Two-thirds of all cases were not diagnosed clinically.

KATZ.

Brown, Margaret E.: The Occurrence of Arteriovenous Anastomoses in the Tongue of the Dog. Anat. Rec. **69:** 287, 1937.

As compared with the arteriovenous anastomoses described by Masson in the human, those found in the dog's tongue are relatively simpler though they agree in their fundamental characteristics. It is suggested that their presence in the dog's tongue may be connected in some way with the elimination of heat upon a rise in body temperature. As far as the author is aware arteriovenous anastomoses have never been seen in the tongue of any other of the laboratory animals.

MONTGOMERY.

Pearl, Felix L.: Angiospastic Claudication: With a Report of Six Cases. Am. J. M. Sc. **194:** 505, 1937.

Treatment should be conservative. If this fails, the response to diagnostic novocaine block will determine the advisability of lumbar ganglionectomy. The

latter procedure should be advised patients who are good risks, are incapacitated by the symptoms, and are relieved by diagnostic block. If vasomotor studies show receding of the vasodilatation level, lumbar ganglionectomy should be done. Poor surgical risks may be treated by alcohol injection of the lumbar sympathetic chain.

The term "angiospastic claudication" is descriptive of the syndrome and distinguishes it from the claudication of occlusive arterial disease.

AUTHOR.

Schlomka, G., and Broich, W.: The Physiologic Variations in Heart Size. Arch. f. Kreislaufforsch. No. 1, 384, 1937.

Roentgenkymography shows that the heart size is not so constant as distant heart plates seem to indicate. A shift of 3.5 to 4 mm. in transverse diameter is not unusual during the heart cycle and in 20 per cent of the cases exceeds 6 mm. and not so uncommonly even 10 mm. The size of the heart both systolic and diastolic varies inversely with heart rate, viz. slowing increases and acceleration decreases it. Increasing diastolic arterial pressure usually causes a decrease in transverse diameter of the heart, and a decrease in pressure causes an increase in diameter. An increase in body weight increases the heart diameter irrespective of the position of the diaphragm. Elevation of the diaphragm readily causes significant increases in the transverse diameter of the heart. These results suggest that kymography should be used as the standard method of measuring heart size and that this be done during moderate respiration.

KATZ.

Raab, W.: Adrenals and Angina Pectoris—Pathogenesis and Roentgentherapy. Arch. f. Kreislaufforsch. No. 1, 255, 1937.

In angina pectoris, except for those cases due to acute coronary closure and other rare forms, the attacks are brought on by the outpouring of adrenalin. Twenty typical cases of angina pectoris are presented in which roentgentherapy of the adrenals was used, apparently successfully, to relieve the attacks.

KATZ.

Ratschow, M.: Vasography as a Test of the Function of the Peripheral Blood Vessels. Fortschr. a. d. Geb. d. Röntgenstrahlen. **55**: 253, 1937.

After the needle is inserted into the lumen of an artery, the flow is stopped for five minutes and then started again while injecting the contrast material. This causes dilatation of all channels and permits visualization of all dilatable vessels. This can also be accomplished by novocaine block of the nerve. Diathermy permits visualization of local regional vessels. The time from the injection until the constant medium leaves the veins is a valuable measure diagnostically. The injection of a contrast medium into a lymph node permits visualization of lymph channels. The use of a contrast medium has permitted the author to demonstrate by means of changes in vein caliber that systolic acceleration of the venous flow occurs in the large systemic and the large lung veins.

KATZ.

White, James C.: Progress in the Surgery of the Autonomic Nervous System. New England J. Med. **217**: 660, 1937.

This is an important eight-page summary, the greater part of which is devoted to a discussion of the effect of autonomic nerve regulation of blood supply. It gives physiologic interpretations as well as useful information of a clinical sort.

Examples are the following: Hemiplegia results in an increase in blood flow in the paralyzed limb, and this may go on to edema of the limb. Preganglionic thoracic sympathectomy is a satisfactory method for production of vasodilatation in the arms—as satisfactory as the older operation of the same sort for the lower extremities. The peripheral vasoconstriction resulting from the use of tobacco does not take place after appropriate sympathectomy. Resection of stellate ganglion for angina pectoris has been followed by a high proportion of favorable results.

The carotid sinus syndrome and some rare but striking vasomotor syndromes of cerebral origins are discussed. Results of various surgical methods for reduction of hypertension are given. An extensive bibliography helps to make this paper n valuable help to a clinician interested in the newer findings in neurologic control of the circulation.

MONTGOMERY.

Duggan, Walter F.: Treatment of Tobacco Amblyopia With Vasodilators. J. A. M. A. **109**: 1354, 1937.

In cases of tobacco amblyopia without optic atrophy, the visual improvement obtained with intramuscular injections of acetylcholine chloride roughly paralleled that obtained with intravenous injections of sodium nitrite.

Visual improvement was more rapid in the patients treated with acetylcholine, but it was greater in the patients treated with sodium nitrite.

The vision of the individual eyes was on the whole more reduced before treatment (more eyes had vision of 20/70 or less) and were on the whole better after treatment (more eyes had vision of 20/30 or better) in the patients treated with acetylcholine. For this reason it would seem that intravenous injections of sodium nitrite are more effective than intramuscular injections of acetylcholine chloride in the treatment of tobacco amblyopia.

This slight but definite difference in potency is probably due to the fact that sodium nitrite is destroyed, inactivated, or excreted by the body less rapidly than acetylcholine, so that its vasodilating effect is active for a longer time.

The conclusion seems unavoidable that either sodium nitrite or acetylcholine, administered parenterally, brings about a more rapid return of vision in cases of tobacco amblyopia without optic atrophy than has been shown to occur in comparable series of cases as a result of treatment with time honored but relatively ineffective methods or drugs. This fact should lend additional support to the hypothesis that tobacco amblyopia is due primarily to a vascular spasm in the visual pathway.

AUTHOR.